SINONASAL MUCORMYCOSIS:

CLINICAL PROFILE AND OUTCOME

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Dedicated

to

my Family

&

Teachers

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COMMIT TO THE LORD WHATEVER YOU DO, AND HE WILL ESTABLISH YOUR PLANS. Successful completion of a task is often less due to individual talent than to the fact that the person has been blessed by the 'GOD ALMIGHTY'

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Dr Porshia Rishi

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ABBREVIATIONS

ABCD	Amphotericin B colloidal dispersion
ABLC	Amphotericin B lipid complex
CRAO	Central retinal artery occlusion
CROM	Cerebro rhino orbital mucormycosis
CROP	Cerebro rhino orbital phycomycosis
CT	Computed tomography
ELISA	Enzyme linked immunosorbent assay
EOM	Extraocular muscles
FDA	Food and drug administration
HSCT	Haematopoitic Stem cell transplant
H&E	Hematoxylin and eosin
HMs	Hematological malignancies
HSCT	Hematopoietic stem cell transplant
ICA	Internal carotid artery
L-AMB	Liposomal amphotericin B
LCB	Lactophenol cotton blue
MRI	Magnetic resonance imaging
NET	Neutrophilic extra cellular trap
PCR	Polymerase chain reaction
PDGFRB	Platelet derived growth factor receptor B
PMNs	Polymorphonuclear leukocytes
PNS	Para nasal sinuses
SAPS	Serine and aspartate proteases
SDA	Sabouraud’s dextrose agar
TNF	Tumour necrosis factor

ABSTRACT

INTRODUCTION: Mucormycosis constitutes the third most common invasive fungal infection following aspergillosis and candidiasis.The Mucormycetes are characterized by the presence of broad aseptate hyphae and are deposited by air borne mode in the nasal cavity and propelled into paranasal sinuses by ciliary action. Mucor, rhizopus and Absidia are the common species.

OBJECTIVE:. To study the clinical presentation, .association of various associated comorbities and to evaluate the outcome of surgical and medical interventions in sinonasalmucormycosis.

MATERIALS & METHODS: the patients admitted with microbiologically /histopathologically proven sinonasalmucormycosis over a period of 1 year (January 2018 to December 2018) undergoing surgical and medical intervention at the department of ENT and Head & Neck surgery Dayanand Medical college & Hospital Ludhiana were studied. The patients were followed up after one , three and six months.

RESULTS: Maximum Patients were in the age group of 41-50 yrs (27.5 %) with the mean age of 46.4 years.Male patients 30 (75%) outnumbered the females (25%). Periorbital swelling (70%), vision loss (67.5%) and rhinnorhea (62.5%) were the prominent complaints. Diabetes mellitus was the underlying disease in 95% of the patients . Middle turbinate (82.5%) and inferior turbinate (82.5%) were the predominant sites involved in our study on nasal endoscopy. VIth cranial nerve (abducent) was the most common cranial nerve involved in 70 % of the patients . 56.4 % of our patients were given Liposomal amphotericin b while conventional amphotericin b was given in 43.6 % of the patients. Radical Nasal debridement was carried out in all the (100%) patients along with orbital exenteration and maxillectomy in 15% of the patients in our study. Survival rate at 6 month follow up was 77.5 % i.e 31 patients survived out of 40 patients. diabetic ketoacidosis did not significantly affect the survival outcome (p value >0.05) in our study. Patients with advanced stage of the disease i.e, nasal, facial and ocular involvement had 25.8 % survival rate in our study.

CONCLUSION: Debridement of the necrotic tissue and sinuses is necessary in all cases of sinonasalmucormycosis . Diagnosis in the early stage depends upon high clinical suspicion.The outcome of the patient with sinonasalmucormycosis depends onearly diagnosis, reversal of the predisposing risk factors, appropriate early surgical debridement and rapid Antifungal therapy

Keywords: Sinonasal Mucormycosis, Debridement, Amphotericin b, Diabetes mellitus

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KEY TO MASTER CHART

Y	Present
N	Absent
PERI ORB	Periorbital Swelling
DM	Diabetes mellitus
ckd	Chronic kidney disease
DKA	Diabetic Ketoacidosis
TB	Tuberculosis
HEP C	Hepatitis C vral marker reactive
HBV	Hepatitis B vral marker reactive
TURB	Turbinate
CRAO	Central Retinal Artery Occlusion
EOM	Extraocular Muscles
VA	Visual Aquity
PUPIL REF	Pupilary Reflex
CULT	Culture
ND	Not Done
NG	No Growth
DNS	Deviated Nasal Septum
CON	Conventional Amphotericin B
LIPO	Liposomal Amphotericin B

KEY TO MASTER CHART

Y	Present
N	Absent
PERI ORB	Periorbital Swelling
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PUPIL REF	Pupilary Reflex
CULT	Culture
ND	Not Done
NG	No Growth
DNS	Deviated Nasal Septum
CON	Conventional Amphotericin B
LIPO	Liposomal Amphotericin B

INTRODUCTION

Mucormycosis, a serious angioinvasive infection caused by common filamentous fungi, that is, mucormycetes, constitutes the third most common invasive fungal infection following aspergillosis and candidiasis.[1] The Mucormycetes are characterized by the presence of broad aseptate hyphae and are deposited by air borne mode in the nasal cavity and propelled into paranasal sinuses by ciliary action. Mucor, rhizopus and Absidia are the common species.

Sinonasal mucormycosis if unrecognized or inadequately treated is an acutely fatal fungal infection. It can infect Central Nervous System, Gastro Intestinal tract and Skin (in burn patient), but best known for it's rhinocerebral presentation, which is initiated with sinonasal involvement and may progress to involve orbit and brain.[2]

Sinonasal mucormycosis is a relatively uncommon disease which primarily affects diabetics, but can occur in any immunocompromised individual such as patient with neutropenia, leukemia, chronic renal failure, long term systemic steroid therapy, protein-calorie malnutrition, solid organ and bone marrow transplantee, leukemia, intravenous drug abusers and having other immunodeficiency states. Once the spores enter the tissue it becomes angioinvasive and shows predilection for internal elastic lamina of arteries, veins and lymphatics. The invasion causes extensive endothelial damage, thrombosis with secondary ischemic infarction and hemorrhagic necrosis. The organism thrives in necrotic tissue and spread by direct extension along injured blood vessels.[3]

The outcome of the patient with sinonasal mucormycosis depends on

(1) Early diagnosis,

(2) Reversal of the predisposing risk factors,

(3) Appropriate early surgical debridement

(4) Rapid Antifungal therapy

Most of the studies done on this emerging disease in India, as well as investigations throughout the world, are retrospective. Due to increase in number of cases and diverse risk factors, there is need of

prospective study so that suspected cases can be diagnosed and treated in a timely manner, which should result in the increase of patient survival. This aim of this dissertation was to study the clinical presentation, epidemiology, therapeutic medical and surgical interventions, various associated comorbidities and outcome of sinonasal mucormycosis.

In the present prospective study, patients admitted with clinical and tissue diagnosis of sinonasal mucormycosis over a period of 1 year (January 2018 to December 2018) were analysed. Surgical and medical intervention was carried out in the department of Otorhinolaryngology and Head & Neck surgery in collaboration with medicine, microbiology and pathology services of Dayanand Medical College & Hospital, Ludhiana.

AIMS AND OBJECTIVES

- To study the clinical presentation of sinonasal mucormycosis.
- To study the association of various comorbities associated with sinonasal mucormycosis.
- To evaluate the outcome of surgical and medical interventions in sinonasal mucormycosis.

REVIEW OF LITERATURE

Mucormycosis is a fungal infection belonging to the order *Mucorales*. Humans acquire the infection predominantly by inhalation of sporangiospores, occasionally by ingestion of contaminated food and due to traumatic inoculation.[1,4] The fungi under order *Mucorales* are ubiquitous, and morphologically appear as broad, aseptate or sparsely septate ribbon-like hyphae. Eleven genera and twenty seven species of *Mucorales* are associated with human infections. Rhizopus arrhizus is the most common agent causing mucormycosis across the globe, followed by Lichtheimia, Apophysomyces, Rhizomucor, Mucor and Cunninghamellaspecies.[5-7]

Mucormycosis is a general term for infections caused by a group of filamentous fungi belonging to the class Glomeromycetes; which due to recent taxonomic reclassification, has replaced the former class of Zygomycetes. In the past, the term Zygomycosis included both Fungi responsible for mucormycosis as well as Entomophthoramycosis. The latter is an uncommon subcutaneous infection encountered predominantly in the tropics. In the revised classification, all agents of mucormycosis have been placed under the subphylum Mucormycotina, whereas agents of entomophthoramycosis are now classified under the subphylum Entomophthoramycotina. As most fungal pathogens associated with mucormycosis are also in the order Mucorales, the term mucormycosis is now considered more taxonomically and clinically appropriate than the previously utilized (and now obsolete) term zygomycosis.[8]

The available literature on sino-nasal mucormycosis has been reviewed from the following aspects:

- Chronological events/historical review
- Epidemiological
- Patho-physiological
- Microbiological
- Anatomical
- Clinical

- Diagnostic techniques
- Medical therapeutics
- Surgical therapeutics
- Prognostic indicators

CHRONOLOGICAL EVENTS / HISTORICAL PREVIEW -

Meyer 1815 recognized the pathogenicity of mucor[9], but it was in 1876 that sufficient data became available to implicate these organisms as causative agents of phycomycosis in humans.[10]

Mucormycosis, also known as Zygomycosis or Phycomycosis, was first described as the aetiological agent in humans by Paultauf 1885, and he coined the term 'mycosis mucorina.[11]In 1943, Gregory et al. associated the predilection of phycomycotic infection in 3 patients of rhinocerebral mucormycosis with diabetes mellitus and provided descriptions of these pathologies that later became recognized as a clinical triad of diabetes mellitus, orbital cellulitis, and meningocerebritis.[12] Harris in 1955 described the first patient with cerebro-rhino orbital mucormycosis (CROM), who fortunately survived the ailment.[13] Earliest descriptions of rhinocerebral mucormycosis, with its association with diabetes mellitus, is given by Gregory et al., 1943; Pillsbury & Fischer, 1977; Meyers et al., 1979; del Real Mora et al., 1983; Abedi et al., 1984.[12,14-17]

Sequele of cerebral involvement in rhinocerebral mucormycosis include cerebral abscess Berthier et al., 1982[18], intracerebral haemorrhage Ho, 1979 [19] and subarachnoid haemorrhage Baker, 1957.[20]

Diamond &Proppe, in 1982 [21] described Intraorbital extension either from the cranium or from the nasal cavity by direct invasion or via the nasolacrimal duct. In a few cases it leads to severe disruption of the globe Blatrix et al., 1970;[22] Albert et al., 1979.[23] There is a characteristic clinical picture of swelling and distortion of the face, markedproptosis,ptosis and early visual loss, all typically unilateral Fleckner & Goldstein, 1969,[24] Pillsbury & Fischer, 1977[14]; Diamond & Proppe, 1982.[21] There is often severe unilateral facial pain, which was earlier attributed to be odontogenic in origin Diamond & Proppe,

1982;[21]Webb et al., 1984[25], associated with a persistent serosanguinous rhinorrhea Smith & Kirschner, 1958;[26] Ferry & Abedi, 1977.[27] Smith & Kirschner in 1958 [26]reported a black crusting ulcer on examination of the nasal cavity, or the palate. Multiple cranial nerve defects because of involvement at the orbital apex were described by Diamond & Proppe,1982.[21]

Cavernous sinus thrombosis is a recognized complication Ferry & Abedi, 1983;[27]Meyers et al,. 1979;[15] Anaissie & Shikhani, 1985,[28] but internal carotid artery thrombosis is much more characteristic, and typically occurs in over a third of cases Landau & Newcomer, 1962.[29] It is usually unilateral, but may be bilateral Wilson et al., 1979.[30]

In 1967 the radiographic findings of mucormycosis of the sinuses were first described by Green et al.[31], who noted three typical signs:nodular thickening of sinus linings, absence of fluid levels, and spotty destruction of the bony walls of the sinuses.

Smith et al 1984[32] concluded that confirmation of zygomycosis should ideally be done by culture in suitable media

Microscopic examination of crushed tissue may provide strong evidence of the correct diagnosis within a few hours Meyers et al 1979.[15]

Computed Tomography scans of the orbit were more characteristic with presence of distortion and displacement of the extraocular muscles and enlargement of the optic nerve Centeno et al., 1981[33]; Diamond & Proppe, 1982.[21] Cerebral changes resemble infarcts or abscesses. Serial Computed Tomography scans may be particularly useful in the assessment of therapeutic response England et al., 1981.[34]

Rapid and effective control of the underlying condition is, if feasible, an important and often crucial prerequisite to therapeutic success Blitzer et al 1980.[35]

The only anti-fungal agent with a proven usefulness against zygomycosis is amphotericin B Blitzer et al 1980[35] and England et al in 1981.[34]

Amphotericin should be used promptly, and the dose titrated to its maximum level as soon as possible. The cumulative dose that may be given is limited by the predictable onset of renal failure.

Radical surgical debridement of necrotic nasal tissue has been emphasised Ferry & Abedi, 1983[27]; Blitzer et al., 1980.[35]

Debridement of the nose, nasopharynx and the face was first reported by Eden & Santos 1979[36] and Rangel-Guerra et al.,1985[37]] while debridement of orbital contents in rhino orbital mucormycosis was first described by Lazzaro & Sloan in 1982.[38]

Adequate surgery of the face may leave a substantial defect, and since such patients may have, on recovery, a good life expectancy, there is a major challenge to the skills of prosthetists Kurrasch et al.,1982.[39] Cures have followed medical treatment alone Hamill et al.,1983[40], but adequate debridement as well provides a much better prognosis Anaissie&Shikhani, 1985.[28]

CHRONOLOGICAL EVENTS IN RHINOCEREBRAL MUCORMYCOSIS

Paultauf -	1885	- First described as the aetiological agent in humans
Gregory -	1943	- Clinical triad of diabetes mellitus, orbital cellulitis, and meningocerebritis
Harris -	1955	-His first patient with cerebro-rhino orbital mucormycosis (CROM), survived the ailment.
Smith & Kirschner	1958	-black crusting ulcer in nasal cavity or palate
Green et al-	1967	- radiographic findings of mucormycosis of the sinuses -
Meyers et al -	1979	- tissue microscopy and KOH staining diagnosis within a few hours
Diamond & Proppe-	1982	-described Intraorbital extension
Smith et al	1984	-culture ideally confirms zygomycosis
Blitzer et al	1980	-only anti-fungal agent useful against zygomycosis - amphotericin b
Blitzer et al	1980	-emphasized Radical surgical debridement of necrotic nasal tissue
Lazzaro & Sloan	1982	-first described orbital debridement

Roden et al 2005[5] reviewed reports of zygomycosis in the British literature since 1885 and analyzed 929 eligible cases. They included in the database only those cases for which the underlying condition, the pattern of infection, the surgical and antifungal treatments, and survival were described.

The first case to be included was reported in 1940. A total of 1049 individual cases of zygomycosis from 1940 through 2003 were identified. Of these, 120 cases were excluded from the database because they did not meet the stringent predefined inclusion criteria. The total database thus consisted of 929 cases (in 1 patient each) reported in 459 published reports. The mean age of patients was 38.8 years; 65% were male. The prevalence and overall mortality were 36% and 44%, respectively, for diabetes; 19% and 35%, respectively, for no underlying condition; and 17% and 66%, respectively, for malignancy. The most common types of infection were sinus (39%), pulmonary (24%), and cutaneous (19%). Dissemination developed in 23% of cases. Mortality varied with the site of infection: 96% of patients with disseminated disease died, 85% with gastrointestinal infection died, and 76% with pulmonary infection died. The majority of patients with malignancy (92 [60%] of 154) had pulmonary disease, whereas the majority of patients with diabetes (222 [66%] of 337) had sinus disease. Rhinocerebral disease was seen more frequently in patients with diabetes (145 [33%] of 337), compared with patients with malignancy (6 [4%] of 154). Hematogenous dissemination to skin was rare; however, 78 (44%) of 176 cutaneous infections were complicated by deep extension or dissemination. Survival was 3% (8 of 241 patients) for cases that were not treated, 61% (324 of 532) for cases treated with amphotericin B deoxycholate, 57% (51 of 90) for cases treated with surgery alone, and 70% (328 of 470) for cases treated with antifungal therapy and surgery. By multivariate analysis, infection due to Cunninghamella species and disseminated disease were independently associated with increased rates of death (odds ratios, 2.78 and 11.2, respectively).They concluded that Outcome from zygomycosis varies as a function of the underlying condition, site of

infection, and use of antifungal therapy. Most patients in this review who were treated with antifungal chemotherapy received amphotericin B or one of its lipid formulations. Amphotericin B has been essentially the only agent active against most Zygomycetes species. As recognition of host groups and their risk factors for zygomycosis increases, earlier intervention with antifungal therapy may improve the outcome of this devastating infection.

EPIDEMIOLOGICAL-

Mucormycosis has emerged as the third most common invasive mycosis following candidiasis and aspergillosis.

A systematic review and meta-analysis of case reports of 851 cases from January 2000 to January 2017 by Jeong et al[41] reported prevalence of mucormycosis as 34% in Europe, followed by Asia 31% and North or South America 28%, Africa 3%, Australia and New Zealand 3%.

In San Francisco, California an active population-based surveillance, from 1992 -1993 showed annual incidence of mucormycosis as 1.7 cases per 1 million individuals (~500 cases per year).[42] The recent 2007 Spain study found a lower incidence ie 0.43 cases/1 million inhabitants, or 0.62/100 000 hospital admissions.[43]

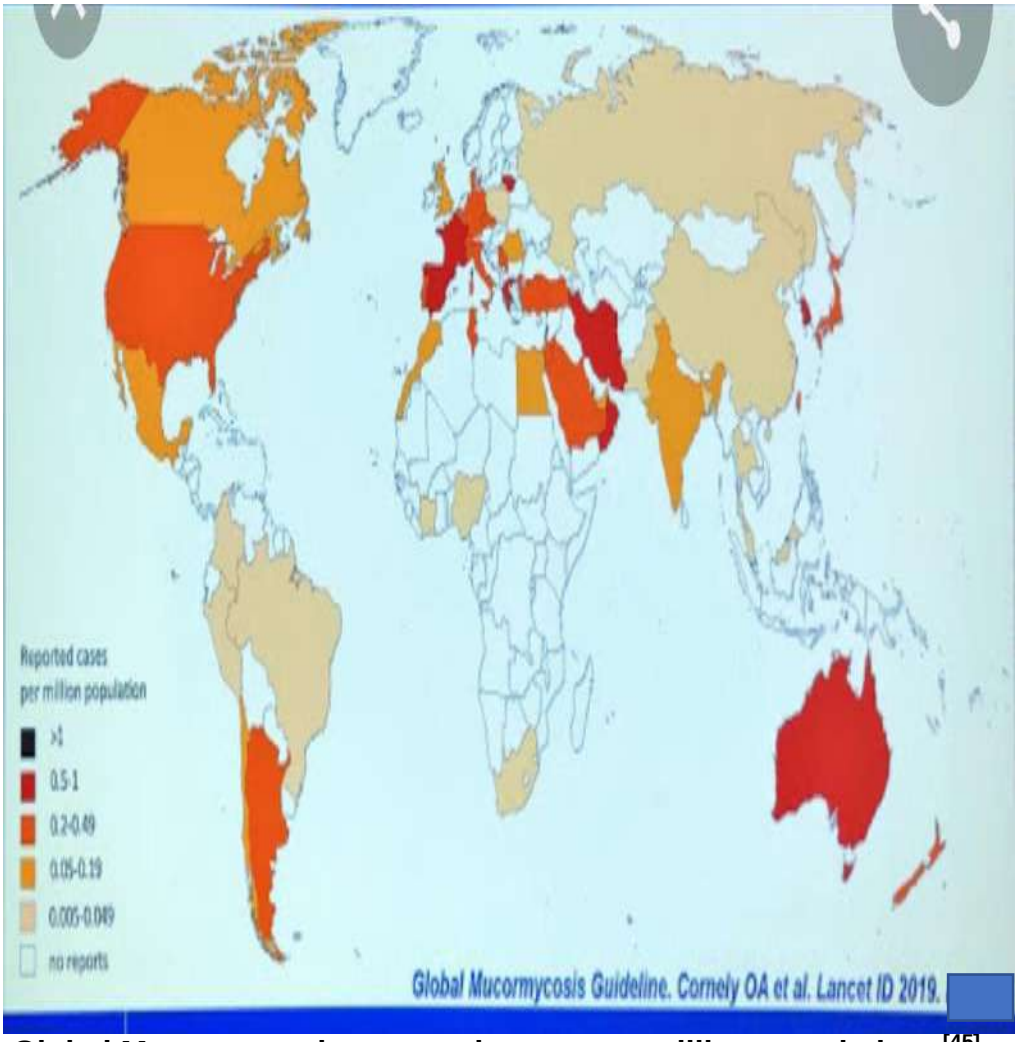
On the basis of clinical presentation and the involvement of a particular anatomic site, mucormycosis can be divided into at least six clinical categories:

(i) Rhinocerebral,
(ii) Pulmonary,
(iii) Cutaneous,
(iv) Gastrointestinal,
(v) Disseminated
(vi) Miscellaneous

The sites of predilectionin invasive mucormycosis are the sinuses 39%, lungs 24%, and skin 19%. Dissemination developed in 23% of these cases Roden et al 2005.[5]

Epidemiology of mucormycosis differs between developed and developing nations. In developed countries, the disease remains

uncommon and, at present, is mostly seen in patients with diabetes mellitus and hematological malignancies (HMs) undergoing chemotherapy and those who have recieved allogeneic stem cell transplants.[44]



Global Mucormycosis reported cases per million populations[45]

In developing countries, more so in India, mucormycosis occurs sporadically in patients with uncontrolled diabetes or after traumatic inoculations.[46]

The common clinical presentations of mucormycosis are rhino-sino-orbito-cerebral, pulmonary, cutaneous, and disseminated. The percentages reported by Jeong et al[41] were 34%, 21%, 20% and 14%, respectively, while in the European study of the Working Group on Zygomycosis the corresponding incidence was 27%, 30%, 26%,

and 15%.[47] In a meta-analysis of all the zygomycosis subjects reported from India, there is overall prevalence of Rhino-orbito-cerebral (58%), cutaneous (14%), pulmonary (6%), disseminated (7%), gastrointestinal (7%) and isolated renal (7%) Diwakar et al 2007.[48]

In the largest review of mucormycosis cases in the british literature, Roden et al [5] compiled 929 cases of mucormycosis from 1885 to 2004 and emphasized that an increasing proportion of immunocompromised patients were reported in the 1980s and 1990s. The paranasal sinuses were the predominant site of infection, presenting in 39% of cases. Rhinocerebral involvement was secondary to paranasal zygomycosis. Independent predictors for sinus zygomycosis were diabetes type 1 (OR, 4.04; 95% CI, 2.36– 6.90), diabetes type 2 (OR, 6.35; 95% CI, 3.89–10.36), and injection drug use (OR, 0.15; 95% CI, 0.04–0.51).There were 283 patients with Central nervous system infection, of which 69% had rhinocerebral infection, 16% had localized cerebral infection, and 15% had hematogenous dissemination of infection from other organs to the brain. Both rhinocerebral infection and localized cerebral infection were associated with a mortality of 62%.

Two reviews of 59 patients with hematological malignancies and mucormycosis Pagano et al., 1997, 2004[49,50] noted that the frequent sites of infection were the lungs (64%) and the orbito-sinus-facial (24%) region.

In a series of 56 patients with cerebral mucormycosis, the rhinocerebral form occurred in 78.5% and all other patients had isolated CNS zygomycosis Sundaram et al., 2005.[51]

Rhinocerebral mucormycosis in patients without the aforementioned predisposing conditions is regarded as a rare occurrence, although it may not be so uncommon as was previously believed. A review of the published English literature revealed more than 70 cases in which none of the known risk factors was present. Furthermore Elinav et al study 2009 revealed [52] that 9.06% of all mucormycosis patients had no predisposing conditions.

Mucormycosis has been reported from all over the world with possible seasonal variation in Mucorales infection. Telmi et al[53] in Israel in

2002 reported 16 of 19 cases of rhino-orbitocerebral mucormycosis (ROCM) which occurred in autumn period.

In the United States, the rate of the disease increased from 0.12 to 0.16 per 10000 patients[37] between January 2005 and June 2014. In India, the incidence of mucormycosis is 70 times higher than the total rate of mucormycosis worldwide with about 0.14 cases/1000 population from January 2010 to December 2014.[38]

Etiology of mucormycosis varies considerably in different countries. In Europe Rhizopus spp. (34%), Mucor spp. (19%), and Lichtheimia spp. (19%) were commonly identified.In India, although Rhizopus species are the most common cause of the disease, Apophysomyces elegans, A.variabilis and Rhizopus homothallicus are emerging species and uncommon agents such as Mucor irregularis and Thamnostylumlucknowense are also being reported Chakrabarti A et al and Chandra j et al [54,55] Another new species of Apophysomyces, namely, A. mexicanus, has been reported from Mexico by Bonifaz A et al in 2014.[56]

Mucormycosis in children was recently analysed in cases extracted from two global registries Panaz et al [57] Fungal isolates included Rhizopus spp. (39.7%), Lichtheimia spp. (17.5%), Mucorspp. (12.7%), Cunninghamellaberthollетiae (6.3%), and unspecified species (23.8%). Underlying conditions were Haematological Malignancy (46%), other malignancies (6.3%), HSCT (15.9%), solid organ transplantation, trauma/surgery and DM (4.8% each) and a variety of other diseases (7.9%); in 9.5%, no underlying medical condition was found. Neutropenia was recorded in 46% of patients. The main sites of infection were lungs (19%), skin and soft tissues (19%), paranasal sinus/sino-orbital region (15.8%), and rhino-cerebral region (7.9%). Disseminated infection was present in 38.1% and mortality was 33.3%.

PATHOPHYSIOLOGICAL ASPECTS –

Inhalation of airborne fungal spores is the primary mode of infection in sinonasal mucormycosis Ribes et al 2000[1] Sporulation occurs in most type of mucorales.The spores are small (3-11micrometre) and easily gain access and lodge in the distal alveolar spaces .The large spores

of more than 10 micrometre size lodge in the nasal mucosa of turbinates and sinuses with subsequent sinusitis Kotoyiannis DP et al 2010.[58]

As the fungi are aerobic, they have a special predilection for the nasal sinuses and the lungs Spellberg et al.[44]

The fungal contamination withstands phagocytosis by macrophages and neutrophils alike, to germinate into hyphae, the latter being an angioinvasive phase of infection Spellberg et al.[44]

Mucormycosis scavenges from the host the element iron for its growth and evades host phagocytic defense mechanisms to access vasculature to disseminate further Spellberg etal.[44]

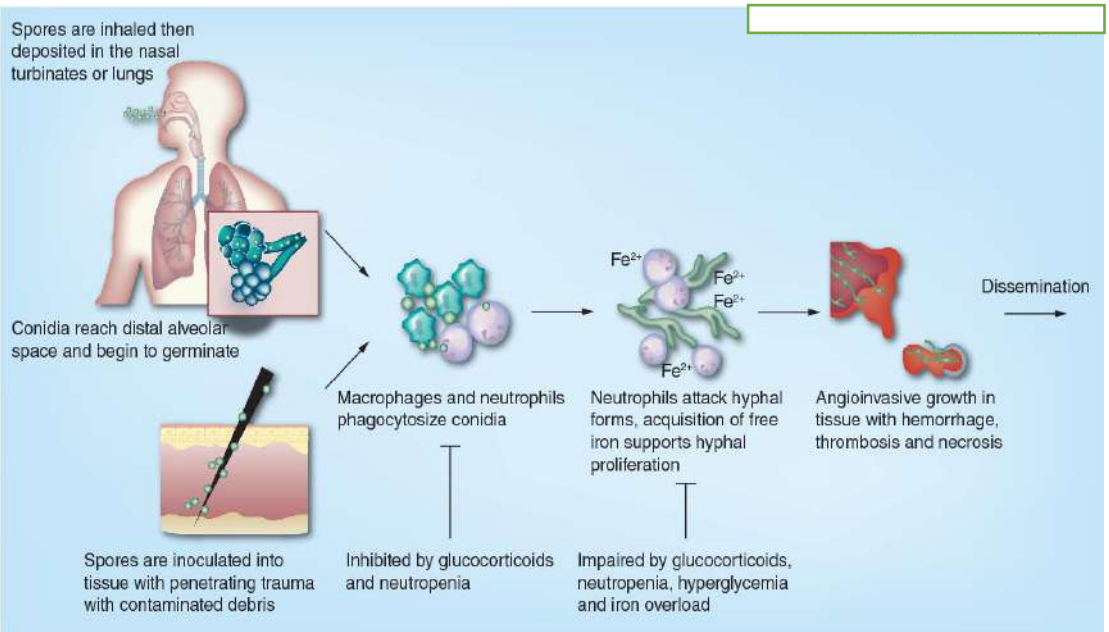
In a normal host defensemechanisms against mucormycosis Spellberg et al.[44]include :

i)Sequestration of iron in serum by specialized iron-binding proteins.

ii)Phagocytes including circulating neutrophils and tissue macrophages.

iii)Endothelial cells which regulate vascular tone and permeability.

Acting in synergism, these mechanisms prevent infection in tissue and subsequent endovascular invasion**.**


Spores are inhaled then deposited in the nasal turbinates or lungs
Conidia reach distal alveolar space and begin to germinate
Spores are inoculated into tissue with penetrating trauma with contaminated debris
Macrophages and neutrophils phagocytosize conidia
Inhibited by glucocorticoids and neutropenia
Fe2+
Fe2+
Fe2+
Fe2+
Neutrophils attack hyphal forms, acquisition of free iron supports hyphal proliferation
Impaired by glucocorticoids, neutropenia, hyperglycemia and iron overload
Angioinvasive growth in tissue with hemorrhage, thrombosis and necrosis
Dissemination

PATHOGENESIS OF MUCORMYCOSIS[59]

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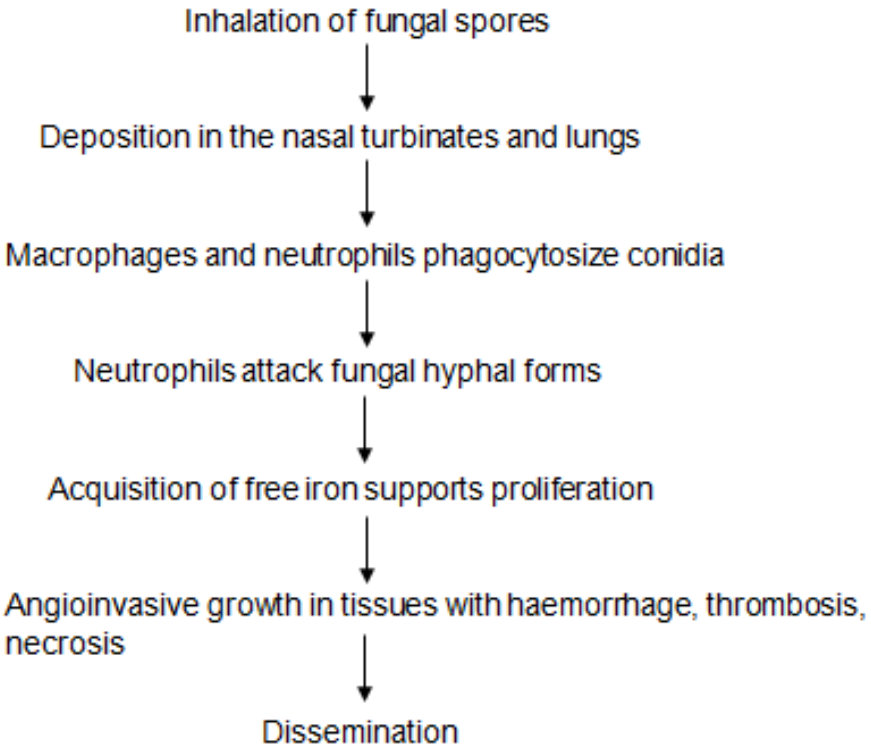
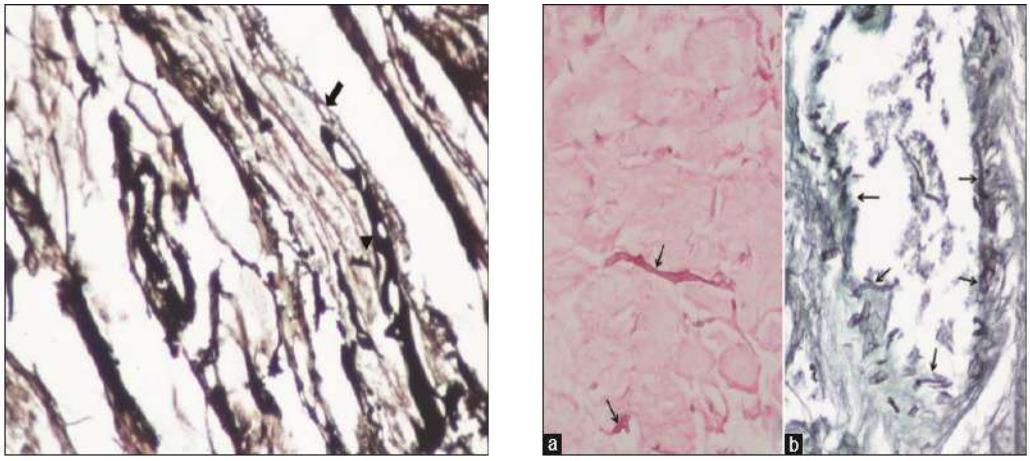
PATHOPHYSIOLOGY OF SINONASAL MUCORMYCOSIS


Inhalation of fungal spores
Deposition in the nasal turbinates and lungs
Macrophages and neutrophils phagocytosize conidia
Neutrophils attack fungal hyphal forms
Acquisition of free iron supports proliferation
Angioinvasive growth in tissues with haemorrhage, thrombosis, necrosis
Dissemination

CHARACTERISTIC ANGIOINVASION

Mucorales characteristically spreads in the tissues by vascular invasion, as blood vessels are the ideal source of oxygen.Mucor is an “angiotropic” fungus with predilection for the internal elastic lamina of the blood vessels, more so the arterial network, and it eventually invades the lymphatics and the venous system.The fungus directly invades blood vessels by inducing arteritis and thrombotic vascular occlusion with consequent ischemia, coagulative and hemorrhagic necrosis, ischemic infarction, endothelial venous damage, aneurysms and pseudo-aneurysms, and ultimately gangrene. Unexpectedly, it results in little inflammation J.N. Schwartz et al 1977[60] When present, the inflammation occurs in a diffusive manner as a spreading, necrotizing reaction that is coupled with mycotic aneurysms.J.N. Schwartz et al 1977[60]



Perineural and Angioinvasion by broad aseptate hyphae consistent with mucor species[61]

PERINEURAL SPREAD

In rhinocerebral mucormycosis, intracranial extension is facilitated by angioinvasion through anterior and posterior ethmoidal vasculature and direct perineural access via the cribriform plate into the anterior cranial fossa Bowen et al[62] .Histology supports perineural extension of disease from cavernous sinus to pons along the trigeminal nerve with no apparent meningeal or intraparenchymal brain involvement McLean *et al*. 1996[63] .Perineural invasion is considered unusual but contrast-enhanced Magnetic resonance imaging studies too have documented

perineural invasion via the trigeminal nerve FM Maclean et al 1996[63],S orguc et al 2005[64], K Parsi et al 2013[65]. Moreover perineural invasion is noted in 90% of tissue biopsies that included peripheral nerves Cornley *et al*. 2014.[66]

Mucor infested tissue may progress from normal pink mucosa to erythematous to violaceous to a necrotic black eschar.Black areas on the palate or nasal mucosa are very suggestive of mucormycosis although they may not be present in 50% of subjects Petrikkos et al.[67]

INTERACTION OF THE MUCORALES WITH THE IMMUNE SYSTEM

i) EPITHELIAL CELLS

Epithelial cells line the outer surface of the skin and alveoli and is first line of contact with the fungal spores Ghuman H et al [68]

The platelet-derived growth factor receptor B (PDGFRB) signalling is the main response of human epithelial cells during infection with Mucorales

In vitro studies on polymeric material exhibit that spores of mucor equally adhere to extracellular matrices like laminin or type IV collagen; under depletion and supplementation of carbohydrates, this attachment does not occur on addition of fibronectin or glycosaminoglycans. Thereby suggests the adherence of the spores to the epithelial basement membrane Bouchara JP et al.[69]

ii) POLYMORPHONUCLEAR LEUKOCYTES

Polymorphonuclear leukocytes (PMNs) or neutrophil granulocytes are an integral part of the innate immune system and regulate the adaptive immune system. Neutrophils check the pathogens by the production of cytokines and the neutrophil extracellular traps (NETs). Chemotactic factors effect the inflammatory response of neutrophils to Mucorale pathogens. These factors are reduced during ketoacidosis and hyperglycemia leading to survival of fungal hyphae of *R. oryzae* in humans. Swollen spores stimulate the neutrophils to produce chemotaxis but not resting or dormant spores; the hyphae suppress the production of neutrophils and thereby chemotaxis. The production of superoxide anion ($O2^{-}$) by intracellular and extracellular neutrophils was raised on contact with hyphae of mucoralean species but was less

compared to *A. fumigatus.* The hyphae of *Rhizopus* spp. activate the Toll-like receptor TLR2 and proinflammatory genes as IL-1B and tumor necrosis factor-alpha (TNFα or TNFA) in neutrophil polymorphonuclear cells and macrophages. Interferon-gamma (IFNγ) and granulocyte-macrophage-colony-stimulating factor (GM-CSF) alone or in combination stimulated the neutrophils to release the TNFα leading to hyphal damage and eradication of mucormycosis. IFNγ reduced the release of IL-8 by neutrophils during their contact with mucoralean fungi Hassan et al 2019;[71]

iii) T CELLS

T cells are part of the adaptive immune system to control infectious diseases, especially mucormycosis.Mucorales-specific T-cells are found only in patients who suffered from mucormycosis but not in other patients that produce interleukins (IL- 4, IL-10, and IL-17) and IFNγ. The cytokines prompt hyphal damage of Mucorales fungi. Treating T-inactivated cells with IL-2, IL-7, or both cytokines enhances the production of Mucorales-specific T cells and their cytokines IL-5, IL-10, IL-13, and even stimulates the production of CD4+ T cells that are a specific to Mucorale antigens. Hassan et al 2019;[71]

iv). NATURAL KILLER CELLS

Natural killer (NK) cells are lymphocyte cells contributing to the immune defense against infected pathogens by reducing dissemination. These cells have shared interfaces with various immune cells in the innate immune system like macrophages and dendritic cells. The hyphae of mucoralean fungi are damaged by stimulated or unstimulated Natural killer (NK) cells, but the Natural killer (NK) cells do not cause any damage to resting (dormant) spores. The protein perforin that is produced by Natural killer (NK) cells has similar structure and function to the complement system, contributes to hyphal damage of mucoralean species. The hyphae reduced the release of various immunomodulatory molecules as RANTES (regulated upon activation, normal T -cell expressed and secreted) and Interferon gamma secreted by Natural killer (NK) cells. This damage is fungal growth dependent

and appears to be more effective in the early stage of infection. Hassan et al 2019;[71]

v) PLATELETS

Platelets adhere to spores and hyphae of mucoralean fungi but damage only to the hyphae Moreover, the hyphal growth is diminished in response to contact with platelets.Hassan et al 2019;[71]

vi) ENDOTHELIAL CELLS

Endothelial cells constitute the internal layer of blood vessels and participate in pathogen recognition and maintaining physiological functions. Endothelial cells are able to phagocytose and to damage the spores of mucoralean fungi. The glucose-regulated protein 78 (GRP78) is a receptor present on the surface of endothelial cells and can specifically recognize *Mucor* spp. but not other fungal pathogens like *A. fumigatus.* In addition, GRP78 mediates invasion and damage of endothelial cells by mucoralean fungi. Increasing the concentration of iron and glucose in diabetic ketoacidosis in mice resulted in enhanced expression of GRP78 on the surface of endothelial cells especially in brain, lung, and sinuses compared to normal mice. Immunochemical investigation of the ethmoidal tissue, infected with mucoralean fungi revealed that GRP78 was highly expressed on endothelial cells and was significantly accessible on the surface of macrophages on the necrotic tissue.Hassan et al 2019;[71]

vii).DENDRITIC CELLS

Dendritic cells (DCs) link the innate immunity with the adaptive immunity as found between the epithelium and the interstitium. Dendritic cells (DCs) move to the site of infection in response to the release of microbial antigens that enhance the immune response. The resting (dormant) spores and germ tubes of mucoralean fungi stimulate the maturation of Dendritic cells (DCs); in contrast, resting spores of *A. fumigatus* do not influence the maturation of Dendritic cells (DCs).Hassan et al 2019;[71]

ROLE OF METABOLIC FACTORS IN PROPAGATION OF MUCORMYCOSIS

1.DIABETES MELLITUS

Combined effects of diabetes, ketosis, and low pH negate the inhibitory property of serum towards spore germination Artis WM et al 1982[72] demonstrated that the fungistatic activity of serum is due to transferrin in the serum, which reduces the free iron available to the fungus for its proliferation .Acidosis temporarily disrupts the capacity of transferrin to bind iron in the serum, thereby reducing the host inhibition of fungal growth. The presence of a ketoreductase in the fungi allows it to utilise ketone bodies in their metabolism; accounting for the increased susceptibility in diabetic ketoacidosis. Waldorf et al 1989,[73] however, could not detect any significant differences in germination of Rhizopus oryzaein normal and diabetic sera with the addition of iron that saturated the total iron binding capacity, nor with the addition of sufficient transferrin to bind all free serum iron. Reduced neutrophil chemotaxis and adhesion to hyphae in diabetes mellitus too have been demonstrated Chinn et al 1982.[74]

Hyperglycemia and acidosis impair the ability of phagocytes to migrate and kill the organisms by both oxidative and nonoxidative mechanisms Chinn et al 1982.[74]

Patients with diabetic ketoacidosis are vulnerable to develop rhinocerebral mucormycosis. Evidence supports that patients in systemic acidosis have elevated levels of available serum iron, due to release of iron from binding proteins in the acidotic medium AW artis etal 1982.[72]

Diabetics with ketoacidosis typically develop the rhinocerebral form of the disease, and rarely develop pulmonary or disseminated disease *KL Peterson et al 1997,*[75] BS khor et al 2003,[76] S *Nithyanandam et al 2003*[77]

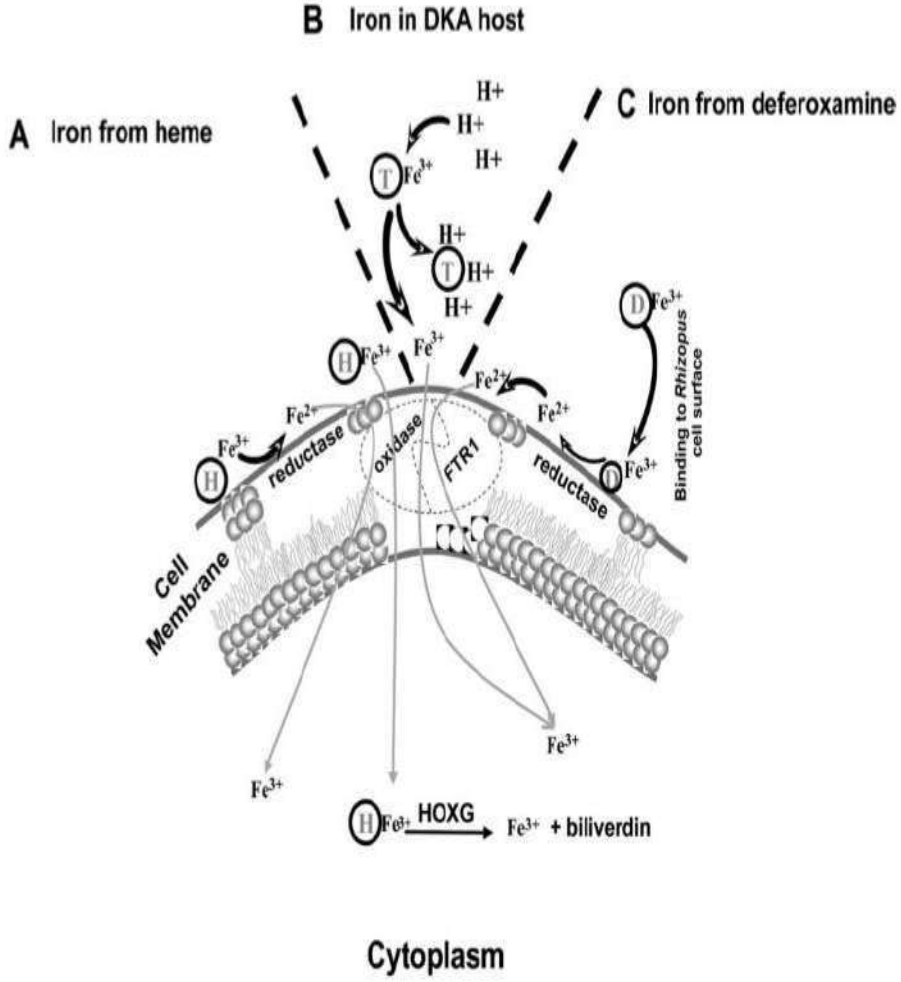
Diwakar *et al*. study of 179 subjects of paranasal sinus mucormycosis report 70% of patients with underlying diabetic ketoacidosis 2007.[48]

Chakrabarti *et al.* 2009 study reported that nearly 50% patients had uncontrolled diabetes mellitus and the association was significant (OR = 9.3; $P \leq 0.001$)(95).[78]

In developing countries like India, rhino sino cerebral mucormycosis is being reported in individuals with underlying diabetes or road side injury Petrikkos et al., 2012.[79]

Balaet al. 2014[80]study of 38 patients of mucormycosis, concluded that diabetes mellitus (56%) was the most common risk factor followed by intramuscular injection (10%), incision and drainage (5%), deferoxamine therapy (2%), followed by trauma (2%). In 24% cases no risk factor was identified.

ROLE OF IRON IN MUCORMYCOSIS



PROPOSED MECHANISMS OF IRON UPTAKE BY MUCORALES DURING MUCORMYCOSIS.Ibrahim et al 2012.[81]

A) Because of the angioinvasive nature of the disease, heme (H) is likely to represent a source of iron to the invading fungus, which either takes up heme intracellularly or strips ferric iron from heme by the action of the reductase-permease system. If heme is transported intracellulary, ferric ironis obtained by the action of heme oxygenase in the cytoplasm.

B) In patients with Diabetic ketoacidosis, proton (H1)–mediated displacement of ferric iron (Fe31) from transferrin (T) increases the availability of iron, which is transported intracellularly by the reductase permease system.

C) Deferoxamine (D) directly chelates iron from transferring, resulting in ferrioxamine (iron-deferoxamine complex). The fungus then liberates ferrous iron from ferrioxamine by reduction at the cell surface. In all cases, iron is transported across the cell membrane by the copper oxidase–iron permease (FTR1) complex.

Iron is required for the growth of a variety of microorganisms, with its availability important in the case of mucormycosis Verweij PE et al 1997.[82] Boelaert et al 1993[83] have shown a marked growth increase of Rhizopus oryzae in iron enriched serum. Of particular clinical importance are studies by de Locht and Boelaert et al 1993[83] showing that deferoxamine treatment for iron overload in fact induces Rhizopus spp. growth as it is utilized by the fungi as a siderophore.

The clinical observation that patients with Diabetic ketoacidosis are uniquely susceptible to mucormycosis lends support to the role of iron uptake in the pathogenesis of the disease. Patients with Diabetic ketoacidosis have elevated levels of free iron in their serum, and such serum supports growth of R. oryzae at acidic pH (7.3–6.88) but not at alkaline pH (7.78–8.38) Boelaert et al in 1993.[83] Furthermore, adding exogenous iron to serum allowed R. oryzae to grow profusely at acidic conditions but not at pH 7.4. Finally, simulated acidic conditions decreased the iron-binding capacity of serum samples collected from healthy volunteers, suggesting that acidosis per se disrupts the capacity of transferrin to bind iron, probably by proton mediated displacement of ferric iron from transferrin.[84] As proof of principle,

animal data showed that mice with Diabetic ketoacidosisare protected from Rhizopus oryzae infection by administration of iron chelators, such as deferiprone and deferasirox Ibrahim et al in 2006,2007 [85,86], which are not used by Mucorales as xenosiderophores.

Another clinical observation highlights the central role of host iron availability in predisposing patients to mucormycosis. Patients receiving dialysis who are treated with the iron chelator deferoxamine are also uniquely susceptible to a deadly form of mucormycosis Boelaert JR et al.[87-90] The bacterial siderophore, deferoxamine, predisposes patients to Rhizopus infection by acting as a xenosiderophore.[91] Deferoxamine strips ferric iron from transferrin and attaches itself on the mold through an inducible receptor, and the iron is transported intracellularly by an active reduction of the ferric form into the more soluble ferrous form.[92] Concordant with these results, administration of deferoxamine worsens survival among guinea pigs infected with Rhizopus but not among those infected with Candida albicans.[91-93]

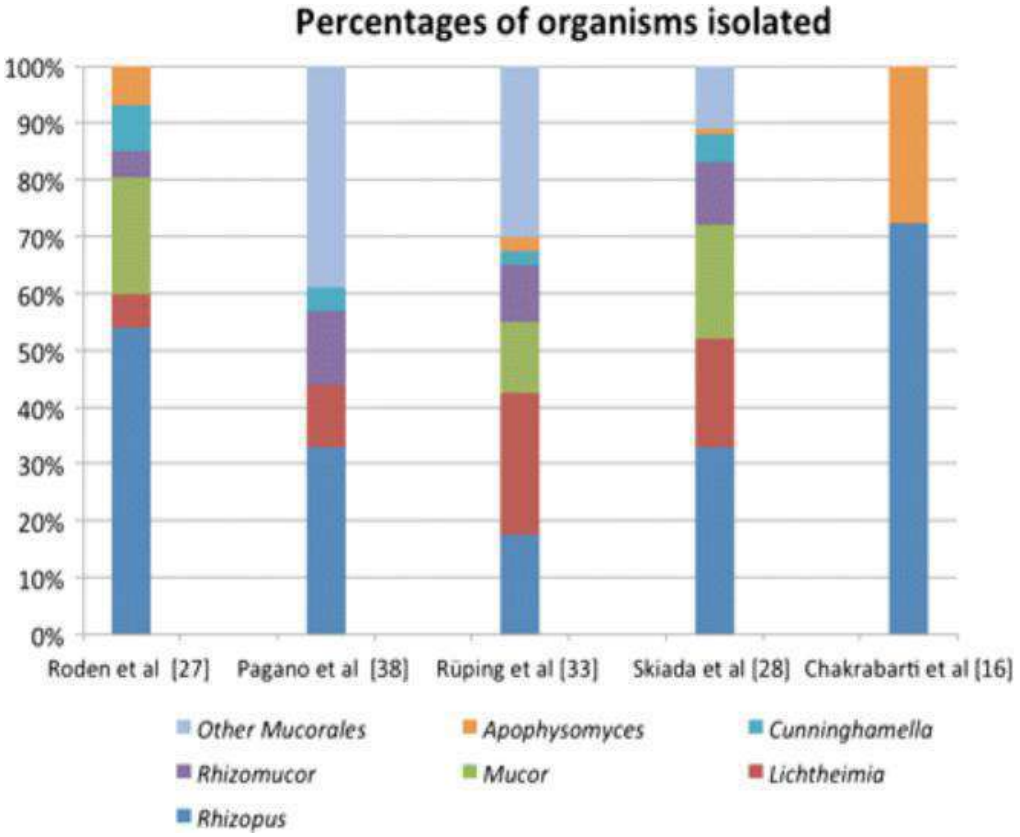
MICROBIOLOGICAL ASPECTS –

Mucormycosis is a general term for infections caused by a group of filamentous fungi belonging to the class Glomeromycetes, which because of recent taxonomic reclassification has replaced the former class name Zygomycetes. In the past, the term zygomycosis encompassed both agents of mucormycosis and fungi responsible for entomophthoramycosis, an uncommon subcutaneous infection encountered predominantly in the tropics.

In the revised classification, all agents of mucormycosis have been placed under the subphylum Mucormycotina, whereas agents of entomophthoramycosis are now classified under the subphylum Entomophthoramycotina. As most fungal pathogens associated with mucormycosis are also in the order Mucorales, the termmucormycosis is now considered more taxonomically and clinically accurate than the previously used (and now obsolete) term zygomycosis.

Inananalysis of 900 humans withmucormycosis, undermentioned genera were identified Roden et al 2005.[5]:

- Rhizopus (47%)
- Mucor (18%)
- Cunninghamella (7%)
- Apophysomyces (5%)
- Absidia species (5%)
- Saksenaea species (5%)
- Rhizomucorpusillus (4%)



Rhizopus and mucor are the predominant species isolated in studies of Roden et al 2005,[5]Pageno et al2006,[94]Ruping et al 2009,[95] Sikada et al 2011,[46] Chakrabarti et al 2006.[47]

Rhizopus oryzae is the predominant pathogen which accounts for 60% of all the forms and 90% of the rhinocerebral involvements Lamia et al., 2008.[96]

Roden et al.2005,[5] reviewed 929 reports of zygomycosis in the British-language literature since 1885 and found co-existing diabetes in 36% of the patients. Zygomycosis had fatal outcome in 44% of them.

Chakrabarti et al. 2006,[46] analyzed 178 cases of Zygomycosis in hospitalized patients in northern India and found co-existing, uncontrolled diabetes in 73.6% of the patients.

Schwartz et al.1977,[60] noticed that cerebro-rhino-orbital phycomycosis (CROP) which was mainly caused by *Rhizopus spp*, occurred predominantly in the individuals with diabetic ketoacidosis.Cerebro-rhino-orbital phycomycosis leads to proptosis, loss of vision, ophthalmoplegia and death secondary to cerebral extension.

Though Rhizopus arrhizus is the most common agent isolated worldwide, Apophysomycesvariabilis is predominant in Asia and Lichtheimia species in Europe. The new causative agents, Rhizopus homothallicus, Mucor irregularis, and Thamnostylumlucknowense are reported from Asia. H Prakash et al 2019.[97]

VIRULENCE FACTORS-

The virulence factors of the Mucorales that are well known and contribute to the immune invasion are –

1) High affinity iron permease

High-affinity iron permease (FTR1) has a role in iron uptake and transport in Mucorales fungi especially during the lack of iron in the environment Ibrahim AS, Gebermariam T, Fu Y et al. 2007.[98] The FTR1 gene is highly expressed during the infection of immunodeficient mice with R. oryzae.

2).Fob 1 and Fob 2 proteins

Fob 1 and Fob 2 proteins are receptors for iron uptake on the surface of the Mucorales and are highly expressed in presence of ferrioxamine that mediates iron transfer through the reductase/permease system without interfering of siderophore-iron complex into the fungal cells.These receptors have a key role in the pathogenesis of R. oryzae in mice treated with the iron chelator deferoxamine. Liu M, Lin L, Gebremariam T et al. 2015 [99]

3).Spore coat protein

Spore coat (CotH) protein is another virulence factor that is detected universally on the spore surface of all Mucorales but not on any other species like A. fumigatus. Cot H plays a key role as invasins in the

pathogenesis of mucormycosis. it disrupts and damages the immune cells. Cot H was found to be a Mucorales specific ligand of the GRP78 receptor.Gebremariam T, Liu M, Luo G et al 2014.[100]

4) Alkaline protease enzyme

Alkaline Rhizopus protease enzyme (Arp) was detected in the culture filtrate of a clinical isolate of R. microsporus var. rhizopodiformis that had a role in enhancing the coagulation process in mucormycosis

5) ADP ribosylation factor

pADP-ribosylation factor (Arf) is a virulence factor that is necessary for growth, fungal dimorphism and virulence in M. circinelloides.[101] A recent study confirmed the lack of a layer composed by rodlet hydrophobins (which is an important virulence factor in A. fumigatus) on the spore surface of Mucorales, which excludes a rodlet-like layer as a virulence factor for the Mucorales.[102]

6.) Calcineurin protein

Calcineurin (CaN) is a calcium and a calmodulin-dependent serine/threonine protein phosphatase and serves as a critical factor in the virulence of Mucorales. It has a tangible role in the transition from yeast to hyphae in M. circinelloides. Lee SC, Li A, Calo S et al et .al 2013,2015.[103,104] Calcineurin is closely linked to protein kinase A activity (PKA). Both are necessary for the pathogenesis of M. circinelloides Lee SC, Li A, Calo S et al et al 2013,2015.[103,104] Disturbance of the Calcineurin-encoding gene resulted in the production of larger spores compared with the wild-type by expressing a spore size dependent role in the virulence

7) Serine and aspartate proteases (SAPs)

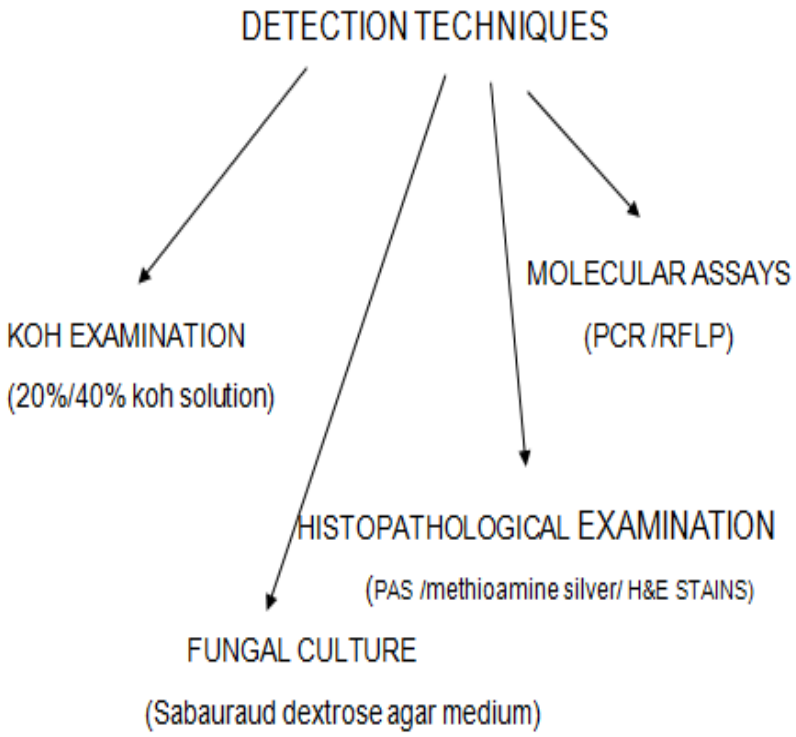
Serine and aspartate proteases (SAPs) were the most common candidates of the secreted proteases in the genome of L.corymbifera with 55% and 36% of the total predicted proteins, respectively.[105] Heat shock transcription factors are predominant in the genome of L.corymbifera compared with other fungal pathogens, a fact that might explain the thermotolerance of Mucorales species. Schwartze VU, Winter S, Shelest E et al.2014 [105]

8) The carbohydrate active enzymes (CAZymes)

The carbohydrate active enzymes represented the majority of the secreted proteins which may possibly play role in the interaction with the environment and the host.[106]

DETECTION TECHNIQUES-

The diagnosis of mucormycosis is vital and treatment should begin as early as possible to reduce mortality. there is no available circulating antigen detection test similar to galactomannan detection for invasive aspergillosis, for the diagnosis of mucormycosis, Although no sufficiently powered trials testing 1,3 beta-D-glucan in different types of mucormycosis have been performed, it is observed that 1,3 beta-D glucan detection test is negative in Mucorales infections. However, these two tests help to rule out invasive aspergillosis, the most frequent differential diagnosis, or in combined Aspergillus and Mucorales infections. Moreover so far, no standardized blood polymerase chain reaction (PCR) test is available. Therefore, analysis of biological specimens from clinically involved sites is mandatory for diagnosis. Every effort should be made to obtain tissue biopsies for histopathology and culture.Skiada A, Lanternier F, Groll AH, et al 2013.[107]



1MICROSCOPIC KOH EXAMINATION

Direct examination in 10% KOH of scrapings from mucosal tissue of the middle and inferior turbinates, aspirated sinus material, sputum, and biopsy material is valuable. The presence of thick-walled, aseptate, and refractile hyphae 6 to 15 µm in diameter, with some hyphae being swollen and distorted, is indicative of the presence of Mucorales fungi.ChanderJ et al 2009.[108]

POTASSIUM HYDROXIDE MOUNTS [108]:-

Composition and preparation of KOH

Potassium hydroxide	10 gm
Glycerol	10 ml
Distilled water	80 ml

10% glycerol is added to solution of 10% KOH to prevent drying. These ingredients are mixed properly and solution stored at room temperature. The wet mount of KOH is prepared by the following two methods:-

a) SLIDE KOH METHOD:-

Nasal mucosa & crusts nasal scrapings are placed on clean glass slide. Tissue Samples, like excised nasal polyp/ nasal or sinus mucosa are first homogenized and then processed further. If suspicion of *Zygomycetes* is there, the clinical specimen should not be homogenized with tissue grinder or mortar and pestle as this may cause leakage in hyphae. Such treatment is suspected to make hyphae nonviable.[109]

A drop of 10% KOH is poured on the specimen and coverslip is placed over it. The slide is heated gently over flame of Bunsen Burner and examined under microscope after few minutes. If specimen is not properly dissolved, it is kept for some more duration in a wet petridish and examined. Overheating is avoided, so that crystals of KOH are not formed.

b) TUBE KOH METHOD:-

Tube KOH method is used for nasal mucosa and excised nasal polyp/ biopsy which are difficult to dissolve. Kwon-Chung KJ, Bennett JE et al

Presumptive identification is based on direct microscopic examination of material from clinical samples.[109]

OBSERVATIONS OF KOH MOUNT PREPARATION: - aseptate fungal hyphae without branching

ASEPTATE FUNGAL HYPHAE[109]

2. FUNGAL CULTURE

A culture result, by itself, is not diagnostic of infection, since Mucorales fungi are common in the environment.[110-113] Culture is ideally carried out of biopsy specimens.[110,113] Exudates and necrotic tissue contain few viable organisms; thus the inoculum from these specimens must be heavy.[113]

Zygomycetes do not survive for more than a few hours at refrigerator temperatures, so if culture is delayed, storage in Stuart's bacteriological transport media at room temperature is recommended.[113]

Sabouraud's dextrose agar or brain-heart infusion agar are commonly used for isolation. Media containing cycloheximide must be avoided, as it inhibits the Zygomycetes.

SABOURAUD'S DEXTROSE AGAR (SDA) WITH ANTIBIOTICS AND WITHOUT CYCLOHEXIMIDE

Composition and preparation [108]

Peptone	10 gm
Dextrose	40 gm

Agar	20 gm
Distilled water	1000ml

The above mentioned ingredients are mixed properly and undermentioned antibiotics are added while boiling but before autoclaving:-

Chloramphenicol	50mg
Gentamicin	20mg

Chloramphenicol or gentamicin are dissolved in 10ml of 95% alcohol and added to boiling medium. The medium is removed from heat source and mixed finely. It is dispensed in tubes and autoclaved at 121ºC for 15 minutes and final pH is adjusted at 5.6. The medium is dispensed in tubes and allowed to cool in slanting position and stored in the refrigerator.

INOCULATION:-

After processing the clinical specimens inoculation is done on SDA media. Inocula are gently implanted into agar at well spaced intervals Each tube having a sterile cotton stopper.

INCUBATION:-

Inoculated tubes containing SDA with antibiotics are kept at two temperatures, 25ºC and 37ºC. All tubes are examined for growth and incubated for upto 3 weeks before recording, no growth.[114]

The gross appearance of the colony serves as the first important step in the recognition and identification of a fungus.

The following characteristics are noted Mime LJR et al 2007[114]:-

- Rate of growth of the colony.
- Texture, colour and shape of the upper thallus.
- The production of pigment on the underside.

Other ideal media for inducing sporulation necessary for speciation.[110,113,115,116] are

-Potato dextrose malt agar

-Czapek solution agar

-Hay infusion agar

Lactophenol cotton blue can be used to better visualize microscopic structures.

LACTOPHENOL COTTON BLUE (LCB) MOUNT is made from growth on culture media to study morphological features of fungal isolates.

Lactophenol cotton blue stain contained following ingredients:- [114]

Phenol crystals	20 ml
Lactic acid	20 ml
Glycerol	40 ml
Distilled water	20 ml
Cotton Blue	0.075 gm

The phenol crystals are dissolved in the liquids by gentle warming and then dye is added.

Lactophenol cotton blue mount (Tease mount) preparation:-

Growth on culture tubes is teased out on a glass slide in a drop of Lactophenol cotton blue stain using two teasing needles. Coverslip is placed over it and examined under microscope. Edges of coverslip are sealed with nail polish to keep it for a longer duration.[117]

Transparency Tape method of preparing LCB mount:-

An elongated drop of Lactophenol cotton blue is placed on a clean microscope slide. A piece of clear vinyl adhesive tape 6-7 cm long is held with forceps and introduced into the culture tube. The centre of the adhesive side of the tape is allowed to touch the colony, lightly under its own weight. The tape is transferred to the slide, placing the area with adhered mycelium on to the lactophenol cotton blue.[117]

Microscopic examination reveals spores and other relevant structures fixed in place by the adhesive. Isolates are identified depending upon the colony morphology and microscopic examination.

OBSERVATION ON FUNGAL CULTURE -

Colonies produce fluffy white, grey, or brown hyphae filling the culture container within 24 to 96 hours. The hyphae are coarse and dotted with brown or black sporangia. It is impossible to distinguish the genera based on colony morphology, as they appear similar.[110,112,113,116]

Identification of genera is based on the presence of aseptate hyphae, the structure of the sporangiophore, and the presence and position of

rhizoids relative to the sporangiophores.[110,112,113,116] Identification to the genus level is possible and can be of great value to the physician in a critical situation.

3. HISTOPATHOLOGICAL SECTIONS

Histological sections exhibit acute suppurative inflammation with focal areas of granulomatous inflammation. There are aseptate hyphae 6 to 50 µm in diameter, branching at 90°. The hyphae invade the adjacent blood vessel walls, producing thrombosis and infarction, but rarely disseminate through the vessels. Staining with Grocott-Gomori methenamine silver is ideal, though Periodic Acid-Schiff and hematoxylin & eosin (H&E) stains can be used.[115,118]

These stains show broad-based, ribbon-like, non-septate hyphae with wide-angle branching (approximately 90). The hyphae are often not well preserved and may become crinkled or gnarled in the tissue sections. This appearance of the hyphal elements is described as resembling “crinkled cellophane”. Cross-sections of hyphal elements often give tissues a vacuolated appearance. These cross-sections vary in diameter and may be confused with yeast cells. The hematoxylin& eosin (H&E) stain should always be confirmed with a more fungus specific tissue stain such as GMS or PAS. The application of optical brighteners in such specimens is also possible.Ribes J A et al in 2000.[1]

Ribes J A et al[1] 2000 documented In comparison to the other hyaline molds that cause disease in man, the zygomycetes stain more poorly or inconsistently with the stains typically used. In H&E- stained tissue sections, zygomycetes generally stain pink with empty or clear lumina. The infected tissue appears frothy due to these clear spaces. Hyphae may be difficult to demonstrate convincingly using this stain. The diagnosis is suggested by the bubbly and frothy appearance generated by the nonstaining hyphal interior than by the hyaline staining of the hyphae themselves. Variability in staining with H&E may be seen. Although the zygomycete elements usually stain pink (eosinophilic) with H&E, purple (hematoxylyniophilic) staining may too be noted. The H&E stain should always be confirmed with a more fungus-specific

tissue stain such as GMS or PAS. Although either of these stains will readily demonstrate zygomycete elements, the relative staining may be less intense than would be seen with other hyaline fungi. There is also some variability in staining intensity within a single clinical specimen. Sporulation in tissues, if it truly does occur, is exceedingly rare.

4. SEROLOGY

Enzyme-linked immunosorbent assays (ELISA),[119]immunoblots,[120] and immunodiffusion tests[121] have been evaluated with variable success. Mucorales specific T cells were detected by an enzyme-linked immunospot (ELISpot) assay in three hematological patients who developed invasive mucormycosis.[122] None of the controls had Mucorales-specific T cells. The use of such specific T cells as surrogate diagnostic markers will be the subject of further studies.

5. MOLECULAR ASSAYS

Molecular based assays include conventional polymerase chain reaction (PCR),[123,124] restriction fragment length polymorphism analyses (RFLP),[125,126] DNA sequencing of defined gene regions,[127,128] and melt curve analysis of PCR products.[129] All assays described above can be used either for detection or identification of Mucorales. The majority of the molecular assays target either the internal transcribed spacer or the 18S rRNA genes.[130,131] Several studies have been done using either formalin-fixed, paraffin embedded or fresh tissue samples[130] yet resulting in different performance. Sensitivity (70–100%) and specificity (not calculated to 100%) varied among the studies performed, with the greatest disadvantage being the low number of patients studied. The efficiency of these in-house assays has not been widely studied, lacks thoroughly clinical evaluation and therefore can't be recommended as standalone, single approach in clinical routine diagnostics.[130]Recent attempts directed at molecular-based diagnosis from blood and serum[132,133,134] have yielded promising clinical data. Molecular-based diagnosis from serum resulted in earlier diagnosis when compared to culture, and over all confirmed culture-proven cases. Presently, molecular-based diagnostic

assays can be recommended as valuable add on tools that complement conventional diagnostic procedures.[130,135,129]

IMAGING STUDIES

Computed tomography and Magnetic Resonance Imaging are invaluable tools which are complementary to clinical evaluation in assessing the extent of disease and diagnosis of complications. Infiltration of the periantral fat planes with rim of soft-tissue attenuation of variable thickness along the walls of the sinuses represent the earliest imaging finding in rhinocerebral mucormycosis and should suggest the possibility of invasive fungal sinusitis. Early paranasal sinus involvement appears as mucosal thickening on CT scans, usually without air/fluid levels. JL Gamba et al 1986.[136]

Addlestone and Baylin et al 1975 [137] reported similar findings, but noted that sinus wall destruction could be extensive rather than spotty, that sclerosis of the osseous walls of sinuses could be seen in chronic cases, and that the typical mucosal thickening in the sinus was smooth rather than nodular.

Areas of increased density, with well defined, markedly hyperdense foci are seen within the inflammatory reaction. This hyperdensity is attributed to calcium phosphate and calcium sulfate deposits in necrotic areas of the mycetoma. Fungal disease of the sinuses is demonstrated radiologically as a nodular mucoperiosteal inflammation leading to homogeneous opacification of the sinus cavity & bony erosion.[138]

Soft-tissue infiltration of the deep face is characterized by obliteration of the normal fat planes in the infratemporal fossa, pterygopalatine fossa & pterygomaxillary fissure. As Silverman et al 1998.[139] described, presence of retroantral, facial and orbital fat stranding indicating the aggressive nature of the infection. In most patients, the extrasinus involvement occurred with intact bones, indicating the perineural /perivascular invasion of the organism, without destroying bone.

Thickening and lateral displacement of the medial rectus muscle are characteristic of orbital invasion. Proptosis occurs because of enhancing soft-tissue mass at the orbital apex and the cavernous

sinuses. Orbital involvement can result in cellulitis, subperiosteal abscess, orbital abscess or cavernous sinus thrombosis.[138]

The 7 variable CT based model proposed by Middlebrooks et al 2015.[140] was found to be effective as a screening tool to triage patients at risk for acute invasive fungal sinusitis The variables included periantral fat, bone dehiscence, orbital invasion, septal ulceration, pterygopalatine fossa, nasolacrimal duct and lacrimal sac.

CT and MR imaging of 43 patients in a study by Jacob therakathu et al [141] at CMC Vellore India in 2018 showed predominant involvement of the ethmoid (37,86%) and maxillary (34,79%) sinuses. Extension to the orbit (32, 76%) and face (24, 57%) preceded involvement of the deep skull base (5,12%) and brain (13, 31%). CT showed minimally enhancing hypodense soft tissue thickening as the predominant finding in involved areas, while MRI showed T2 isointense to mildly hypointense soft tissue thickening and heterogeneous post contrast enhancement as the main finding. Bone erosion was seen less often (17, 40%), with rest (26, 60%) of the patients showing extrasinus extension across grossly intact appearing bones on imaging

Due to the angio invasive nature of the disease, skull base osteomyelitis and bone involvement is usually not seen or seen only late in the disease[142] Only few case reports of chronic mucormycosis involving bone are available L.L. Chan et al 2000 [142,143]

Magnetic Resonance imaging may be used in the initial evaluation of complicated sinusitis because of its ability to better depict advanced disease involving the orbit or brain, extraaxial space and meninges, and the cavernous sinuses.[138]

Magnetic Resonance imaging, especially the nonenhanced T1 weighted images are sensitive to minor pathologic abnormalities in the skull base. The characteristic finding is lost T1 signal hyperintensity of skull base marrow fat.[138]

An aggressive sinonasal and orbital inflammatory process was reported by Mnif and colleagues 2005,[144] who suggested that the association between orbital cellulitis and sinusitis in the context of immunosuppression should prompt the diagnosis of mucormycosis.

Mohindra et al. 2007[145] have shown that Magnetic resonance imaging can detect cavernous sinus invasion and vascular complications such as thrombosis and ischemia According to Razek and Castillo 2009[146] involvement of cavernous sinus appears hypointense on T1 and T2 with intense inhomogeneous post contrast enhancement

CLINICAL PROFILE–

The clinical progression of rhino-cerebral mucormycosis is classified into 3 stages Mohamed, Mostafa S et al 2015.[147]

stage 1 - infection of nasal mucosa and paranasal sinuses

stage 2 - orbital involvement leading to superior orbital fissure syndrome and orbital apex syndrome

stage 3 - cerebral involvement leading to cavernous sinus thrombosis, occipital and frontal lobe infarctions

STAGE-1

Clinical symptoms usually begin as nonspecific malaise and headache, progressing to acute sinusitis, facial edema and pain, rhinorrhea, and eventual ophthalmoplegia, blindness, and lethargy.[148] This can make differentiation from the more common and less morbid bacterial sinusitis challenging, and often these patients fail antibiotic treatment prior to histopathologic diagnosis of fungal sinusitis and commencement of appropriate antimicrobial therapy.[149] The only disease specific finding described in the relative literature is blackened necrotic eschars of the nasal mucosa or palate.[150] However, in large case series it has been noted in less than half of the patients.[67] Furthermore, it should be noted that initial appearance of the inflamed nasal mucosa may be normal[151] An erythematous phase develops at a later stage and the formation of necrotic eschars rather represents local disease progression with blood vessel thrombosis and tissue infarction.[152] Raasi S J et al in 2009 described the most common signs and symptoms of rhino cerebral mucormycosis as fever, rhinorrhea, facial erythema and oedema, and very pale nasal mucosa.[153]The most frequent otorhinolaryngological signs and symptoms were nasal obstruction, pale turbinates and nasal crusting (80%), facial hypoesthesia (60%) and facial paralysis (40%), while 1 patient (20%)

had necrotic eschar in the palate by Hernández OP et al in 2013.[154] Yohai et al[150] reviewed 145 case reports of Rhino orbito cerebral mucormycosis and reported facial swelling (30%), facial parasthesias (20%), nasal ulceration or necrosis (48%), palatal necrosis (32%), and infranuclear facial palsy (22%). Similarly, Ferry et al[155] reported black eschar of skin, nasal mucosa, or palate in only 19% of their patients.

STAGE-2

Mucor sinusitis can rapidly progress from isolated sinus involvement to direct orbital extension leading to pain, ptosis, proptosis, ophthalmoplegia, and eventual blindness.[148,149] representing involvement of the orbital contents either by infection or vascular compromise. In their retrospective review by Bhansali et al[156] of 35 patients, ophthalmoplegia (89%), proptosis (83%), loss of vision (80%), chemosis (74%), periorbital swelling (66%), and periorbital pain (43%) were the most frequent ophthalmologic signs/symptoms associated with mucormycosis. Corzo-Leon et al[157] proposed an algorithm for the diagnosis of rhinocerebral mucormycosis in diabetic patients. The list of signs and symptoms that should be considered to be “red flags” includes a cranial nerve palsy, diplopia, sinus pain, proptosis, periorbital swelling, orbital apex syndrome, and ulcers of the palate. 100% of the patients began with ophthalmological symptomology in a retrospective, longitudinal, descriptive study, conducted by Hernández OP et al in 2013 with orbital apex syndrome being found in 60%.of the patients.[154]

STAGE-3

Intracranial extension occurs in 80% of cases and causes encephalopathy, cerebritis, and angioinvasion leading to cavernous sinus thrombosis and cerebrovascular accidents.[142,158,148] Early diagnosis and subsequent treatment has been shown to portend higher survivability.[149,159,148] The Contralateral ophtalmoplegia suggests cavernous sinus thrombosis. Progression of the infection to central nervous system is heralded by development of confusion and disorientation, with bloody nasal discharge also reported as a potentially early sign of disease extension to the brain. Central nervous

system damage may also result from cavernous sinus thrombosis and internal carotid artery encasement leading to cerebral infractions and hematogenous dissemination of the disease to other organ sites.[160]Yohai et al[150] reported altered sensorium (29%), hemiparesis (17%), and meningeal signs (11%) in their patients .

Vaughan C et al 2018[160] observed the common non-ophthalmic symptoms include fever (26–44%), headache (5–25%), facial swelling (27–34%), facial pain (3–22%), nasal discharge (2–18%), epistaxis (0.5–9%), sinusitis (1–26%), hemiplegia (0–4%), nasal ulceration (3–38%), palatal eschar (5–14%), tooth ache (0.5–3.5%), facial numbness (3–7%), facial nerve palsy (0.5–11%), bone destruction and altered mental status (2–22%). Orbit is involved by direct extension of the disease from the paranasal sinuses. The ophthalmic signs and symptoms include eye pain, decreased vision, ophthalmoplegia (15–29%), proptosis (11–16%, chemosis (4.5–9%), ptosis (3.5–18%), orbital cellulitis (2–16%), periorbital discolouration and necrosis.

ANATOMICAL ASPECTS–

Mucormycosis is characterized by a mycotic infiltration of the mucous membrane of the nasal cavity and the paranasal sinuses. The frequent sites of involvement, are adjacent to the middle turbinate, the septum andthe inferior turbinate.

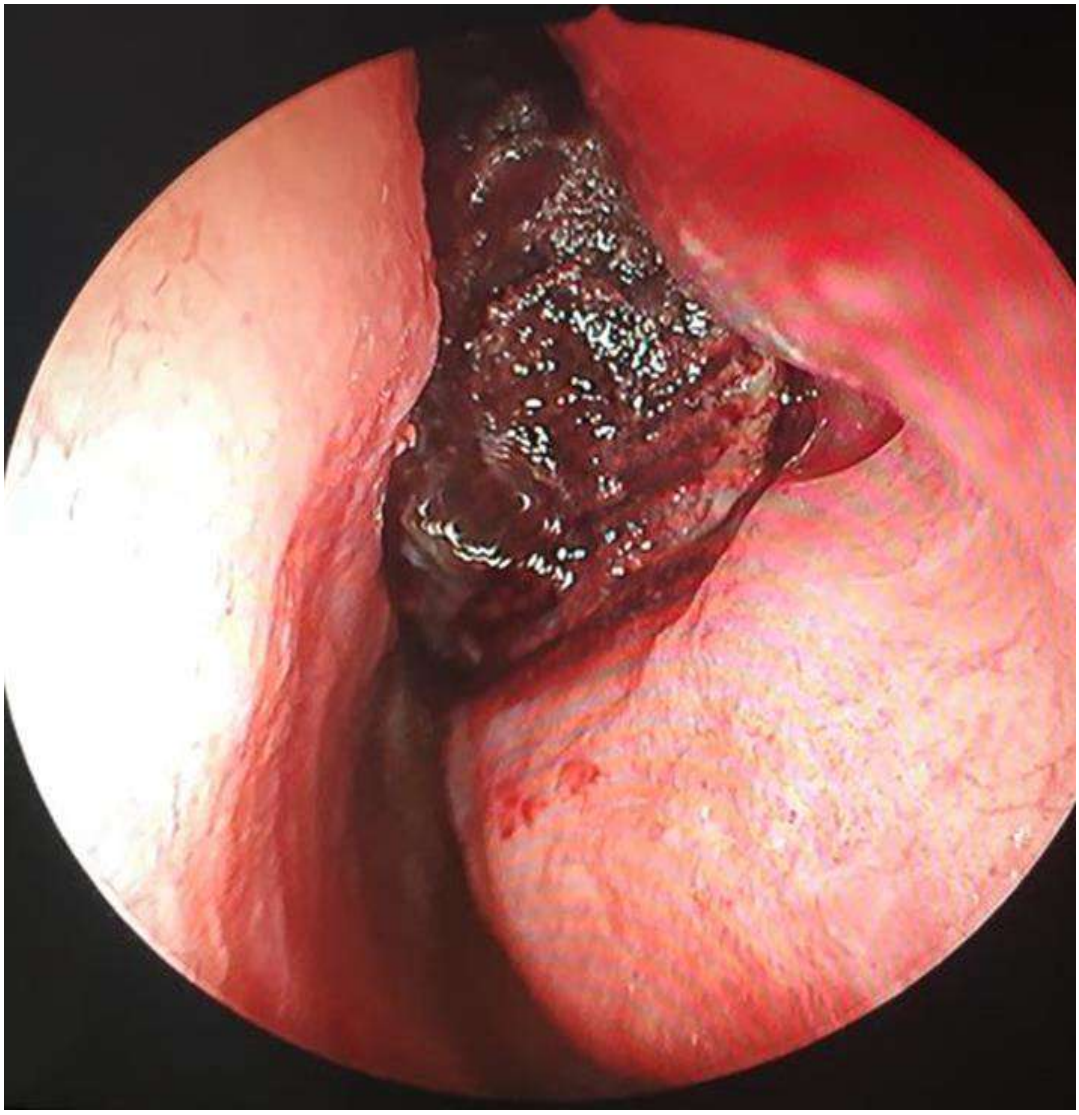
The middle turbinate exposed to the maximal volume of airflow and being the primary nasal air filter, there is increasing likelihood of fungal seeding at this site.[161] Mucosal disruption, mucociliary damage, and shift in the normal mucosal flora are likely at the middle turbinate and meatus secondary to bacterial sinusitis, allergy, drying secondary to oxygen via nasal cannula, and mechanical damage due to nasogastric tube.[162] Damage to the middle turbinate facilitates fungi to initiate the invasive process.The common site of fungal invasion is the middle turbinate in 62% of patients whose nasal tissue have undergone biopsy Gillespie et al 1998.[163]

Paranasal sinuses affected in decreasing order are the maxillary sinus (100%), anterior ethmoidal sinus (87%), posterior ethmoidal sinus

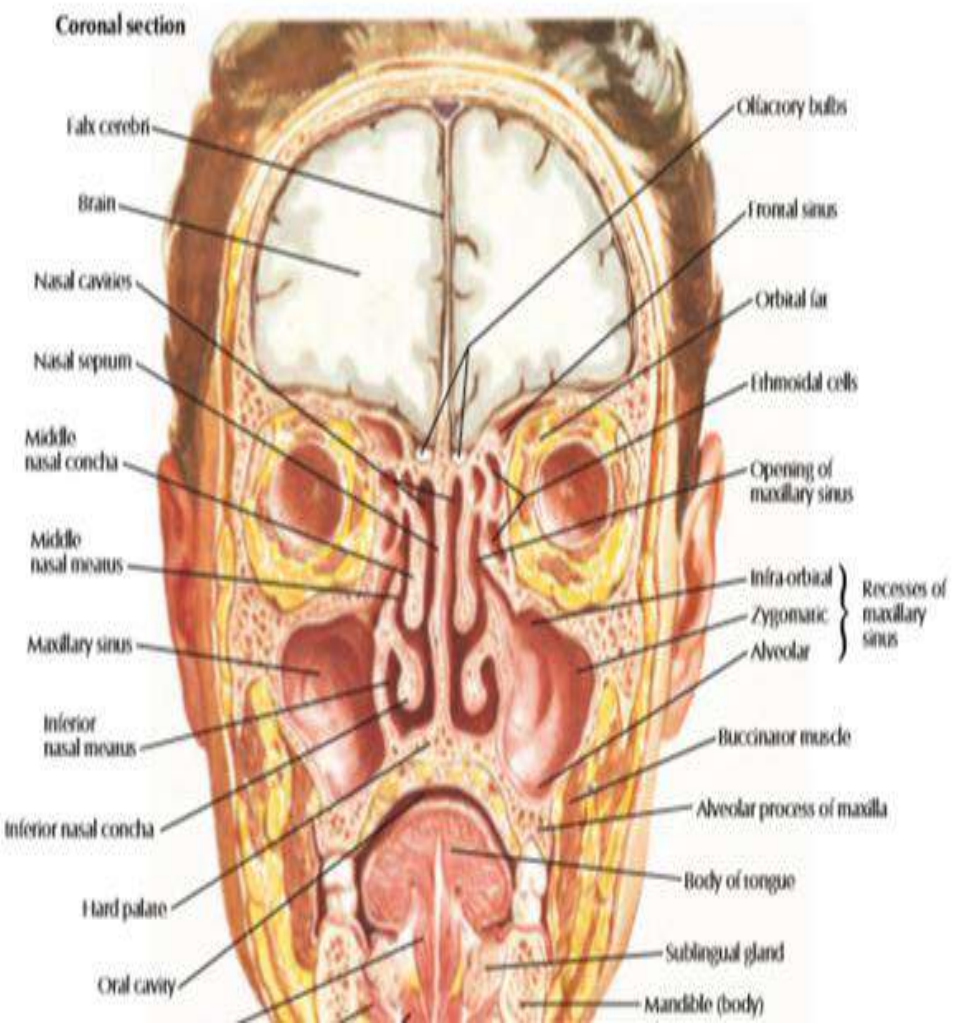
(53%), sphenoidal sinus (26.5%) and the frontal sinus (13%) Prado-Calleros et al 2016.[164]

The Bhansali et al study of 35 patients of Rhino orbital mucormycosis documented ethmoid 86% and maxillary 80% sinuses as being frequently involved.[156]

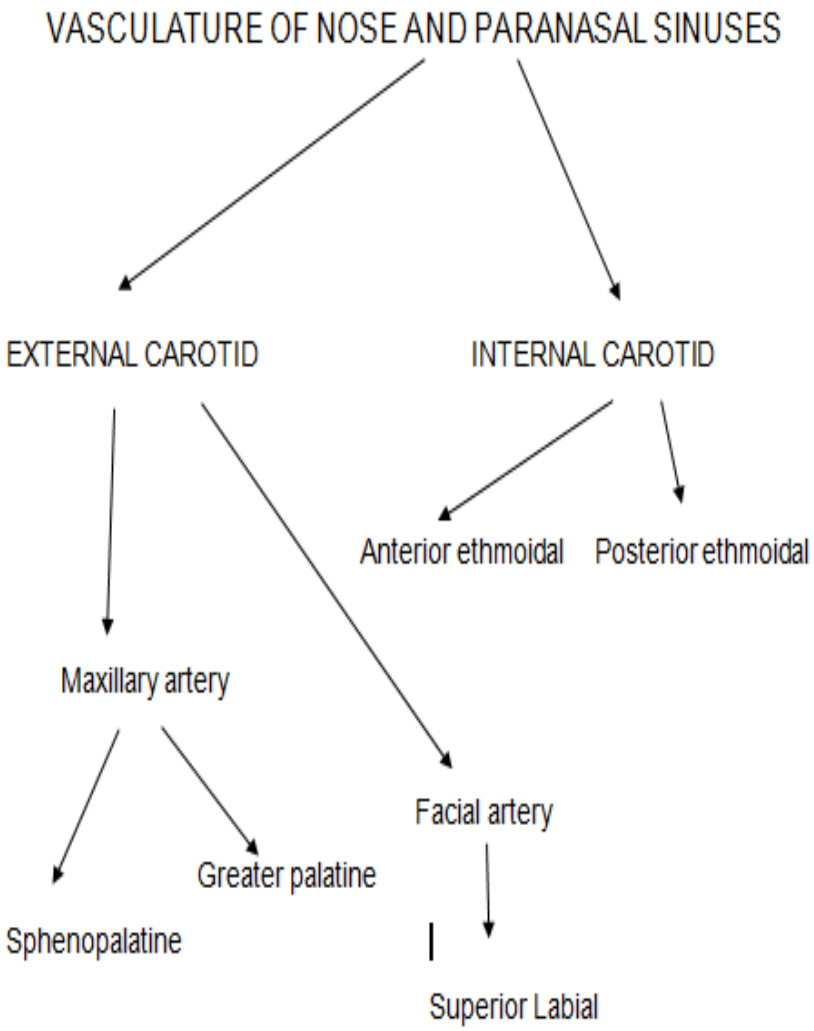
On germination, the invading fungus spreads inferiorly to invade the palate, posteriorly the sphenoid sinus, laterally the cavernous sinus and the orbits, or cranially the brain.Hosseini SM, Borghei P 2005.[165]



NECROTIC MIDDLE TURBINATE LEFT NASAL CAVITY



CORONAL SECTION SHOWING PARANASAL SINUSES[166]

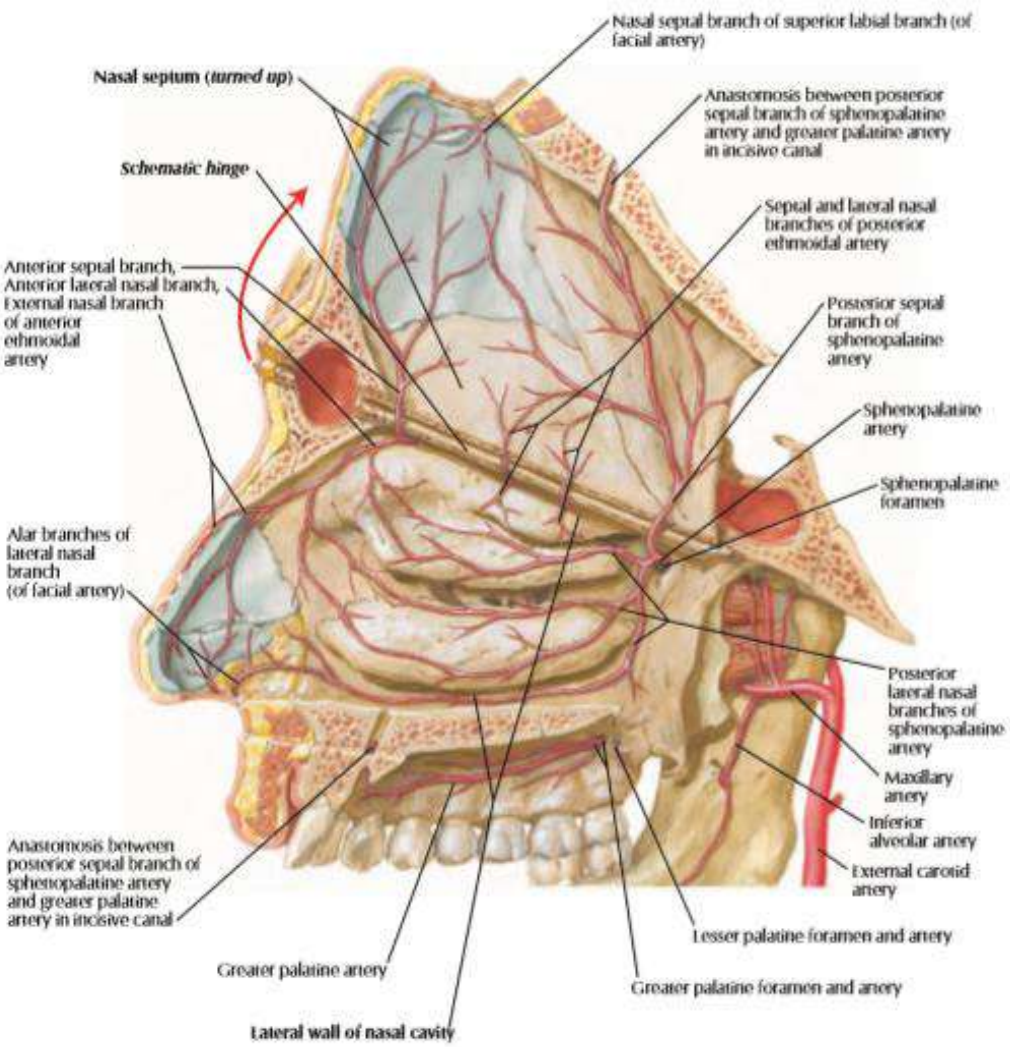

VASCULATURE OF NOSE AND PARANASAL SINUSES
EXTERNAL CAROTID
INTERNAL CAROTID
Anterior ethmoidal
Posterior ethmoidal
Maxillary artery
Facial artery
Greater palatine
Sphenopalatine
Superior Labial

NASAL AND PARANASAL SINUS VASCULATURE

The external and internal carotid arteries are responsible for the rich blood supply of the nose. The sphenopalatine artery, branch of the maxillary artery and thus external carotid artery, supplies the postero-inferior septum and the antero-inferior face of the sphenoid sinus, as well as the posterior halves of inferior and middle turbinates.

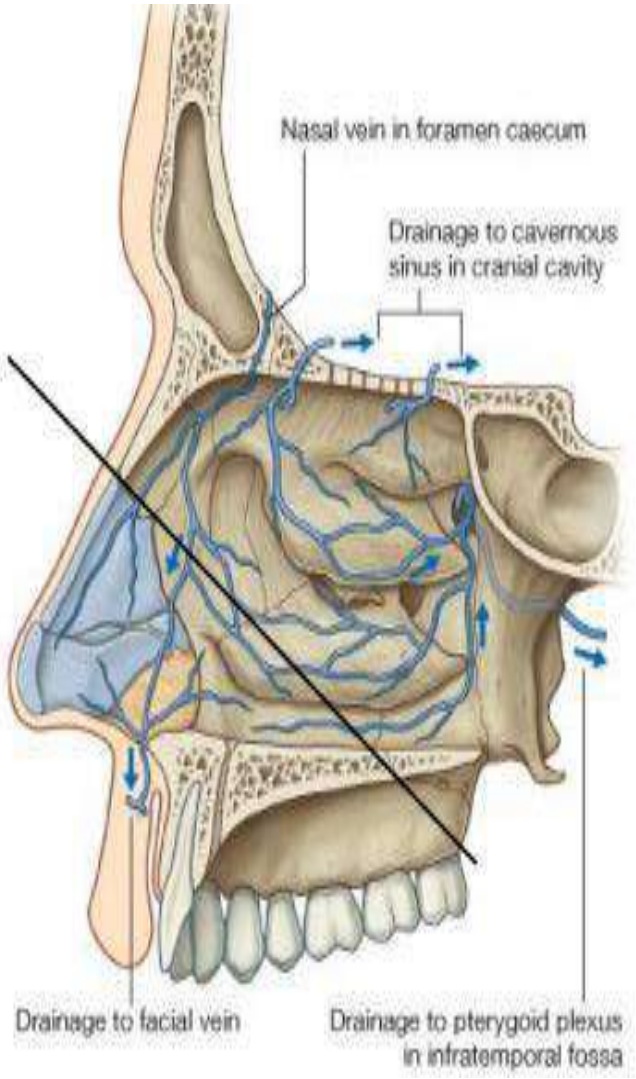
The greater palatine artery, a branch of the maxillary artery supplies the antero -inferior portion entering the nasal cavity via the incisive canal. The superior labial branch of the facial artery contributes anteriorly, to the Kiesselbach's plexus, which is composed of unusually long capillary loops. The internal carotid artery supplies the septum superiorly through the anterior and posterior ethmoidal arteries

There is considerable overlap between the internal and external carotid arterial systems on each side and between the right and left sides. The internal carotid artery contribution is through the ethmoidal arteries which supply the superior lateral nasal wall. The external carotid artery distributries namely the branch from facial artery supplies the lateral wall anterior to middle turbinate; and the greater palatine artery supplies part of the lateral wall adjacent to the palate.[167]


Nasal septal branch of superior labial branch (of facial artery)
Nasal septum (turned up)
Anastomosis between posterior septal branch of sphenopalatine artery and greater palatine artery in incisivo canal
Schematic hinge
Septal and lateral nasal branches of posterior ethmoidal artery
Anterior septal branch, Anterior lateral nasal branch, External nasal branch of anterior ethmoidal artery
Posterior septal branch of sphenopalatine artery
Sphenopalatine artery
Sphenopalatine foramen
Alar branches of lateral nasal branch (of facial artery)
Posterior lateral nasal branches of sphenopalatine artery
Maxillary artery
Inferior alveolar artery
External caroid artery
Anastomosis between posterior septal branch of sphenopalatine artery and greater palatine artery in incisive canal
Lesser palatine foramen and artery
Greater palatine artery
Greater palatine foramen and artery
Lateral wall of nasal cavity

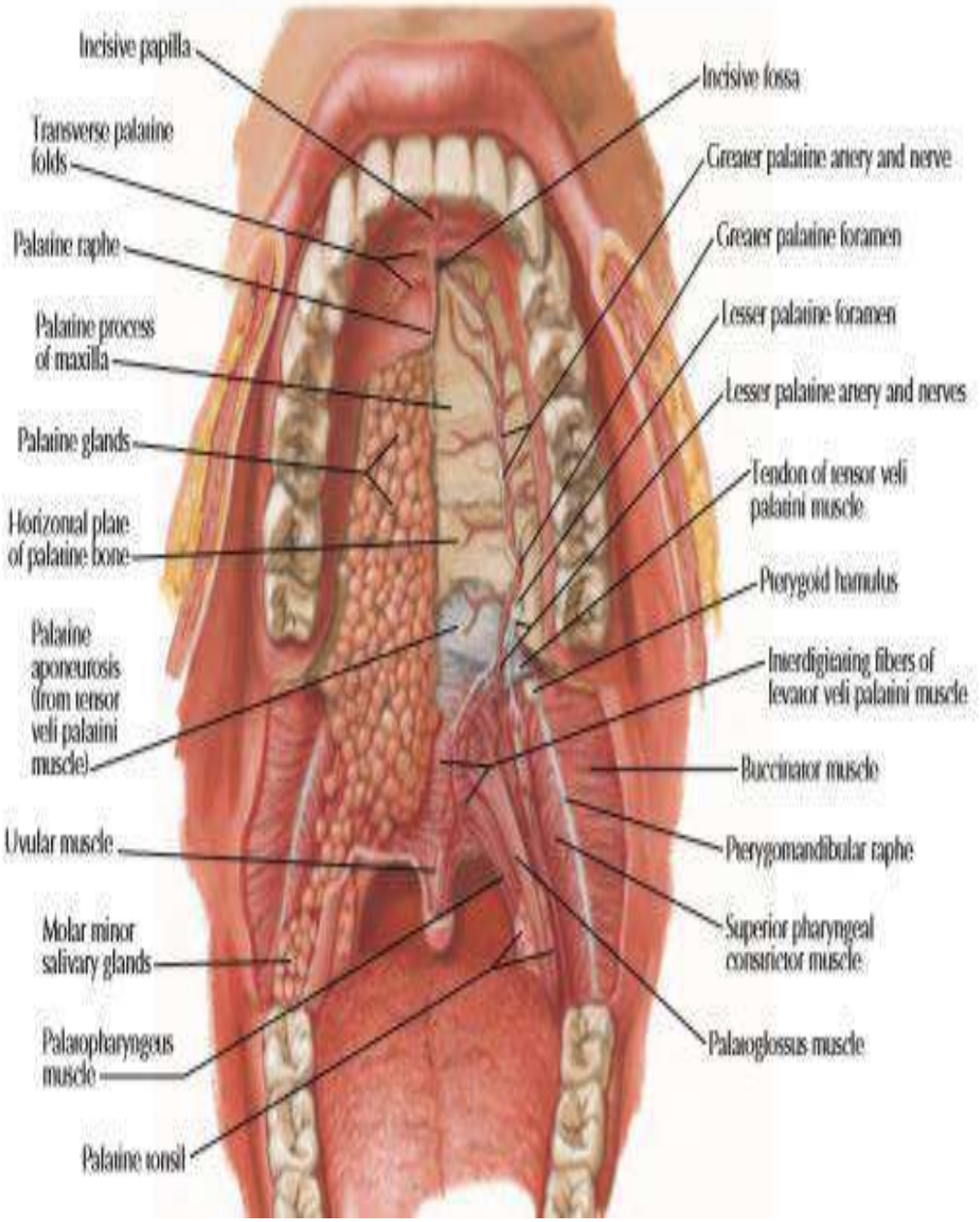
NASAL AND PARANASALVASCULATURE[166]

The nasal vascularity is well-developed and is augmented by the cavernous plexus embedded in the lamina propria, in particular on the inferior and middle turbinates, and is under autonomic regulation. The veins of the plexus are between 0.1 and 0.5 mm wide and anastomose with each other. Numerous arteriovenous anastomoses are found in the deep mucosa and around the glands. Venous drainage is to the sphenopalatine veins and into the pterygoid venous plexus posteriorly and anteriorly into the facial and ophthalmic vessels. Intracranial drainage is to the ethmoidal veins to veins on the dura and to the superior sagittal sinus via the foramen caecum.[167]

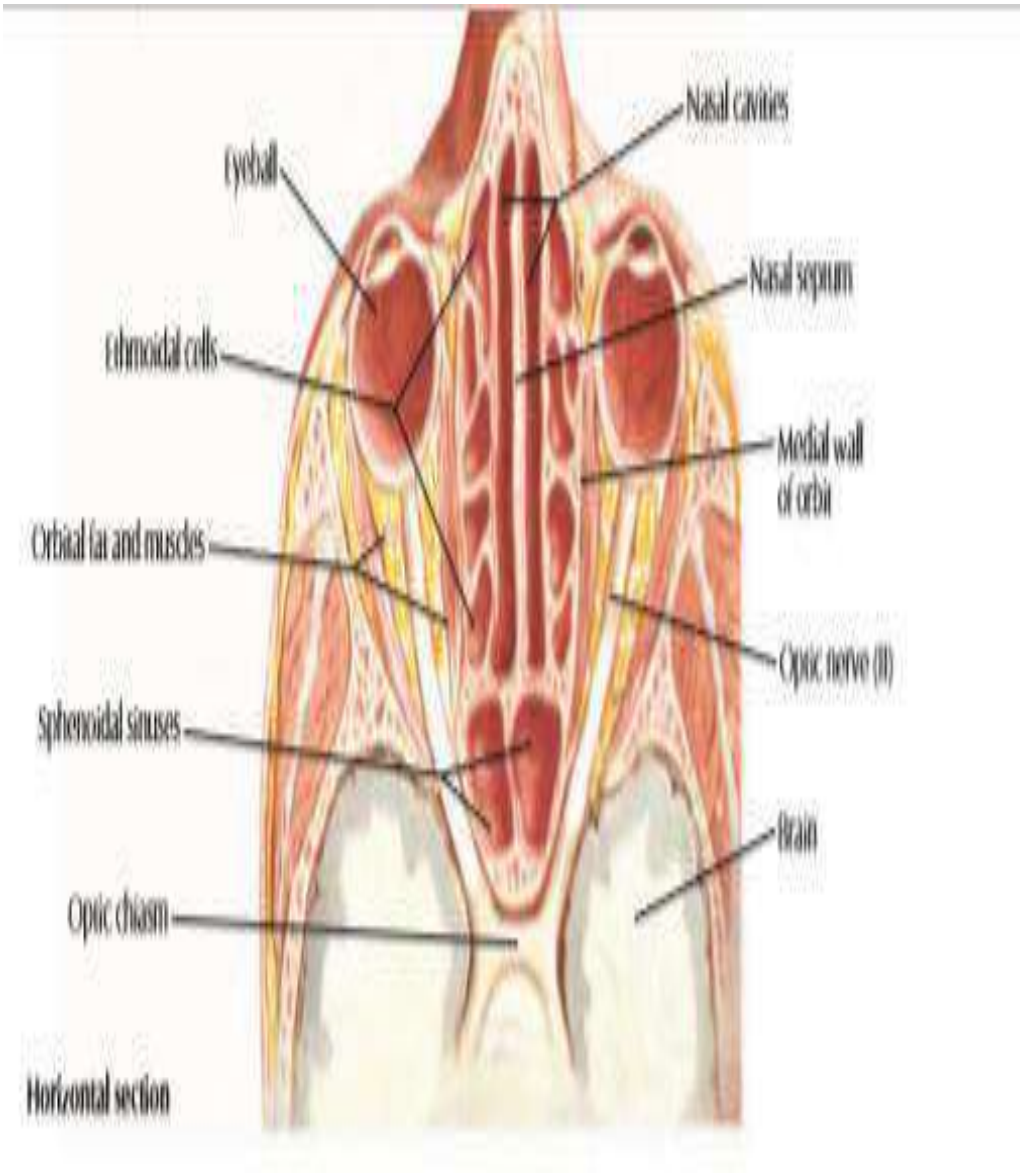

Nasal vein in foramen caecum
Drainage to cavernous sinus in cranial cavity
Drainage to facial vein
Drainage to pterygoid plexus in infratemporal fossa

NASAL AND PARANASAL SINUS VENOUS DRAINAGE[166]

Angioinvasion is through the greater and lesser palatine vessels branches of maxillary artery, ascending palatine artery branch of facial artery, and the ascending pharyngeal artery of the external carotid artery.[168]



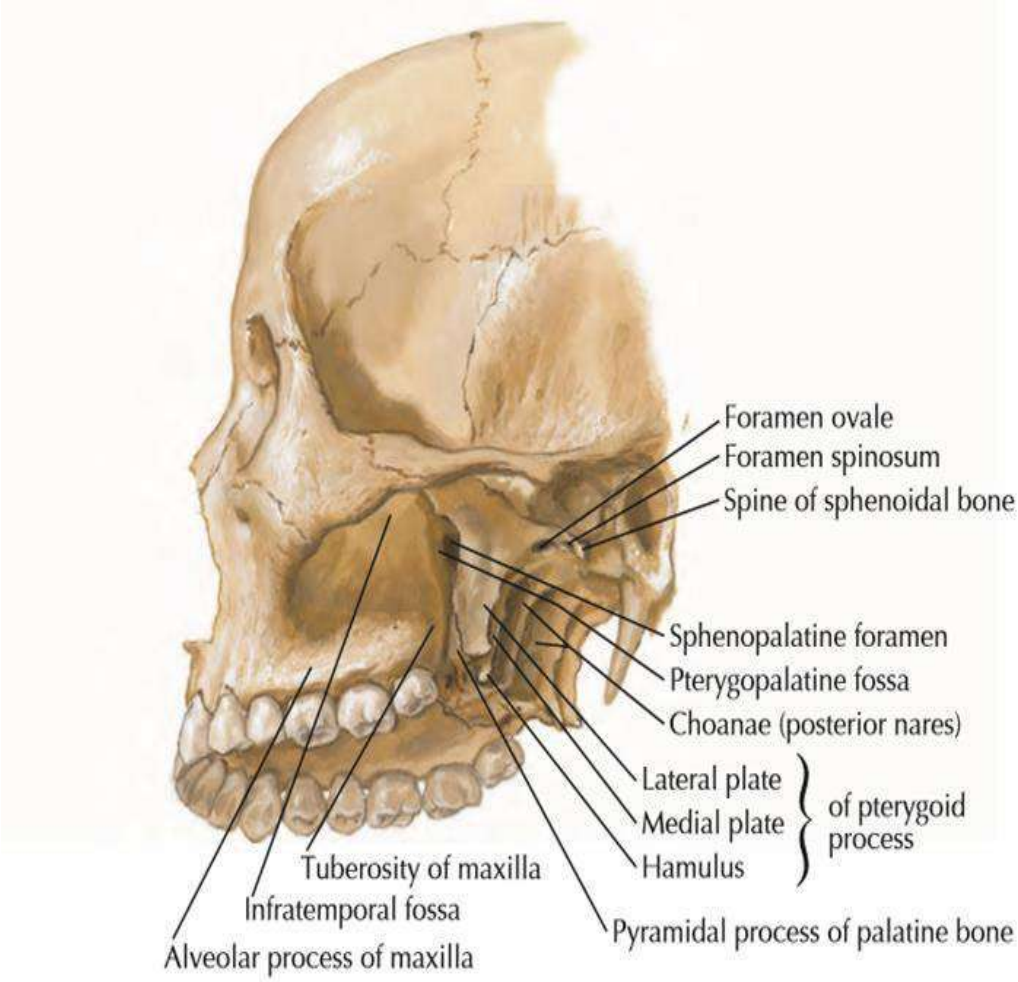
VASCULATURE OF PALATE[166]



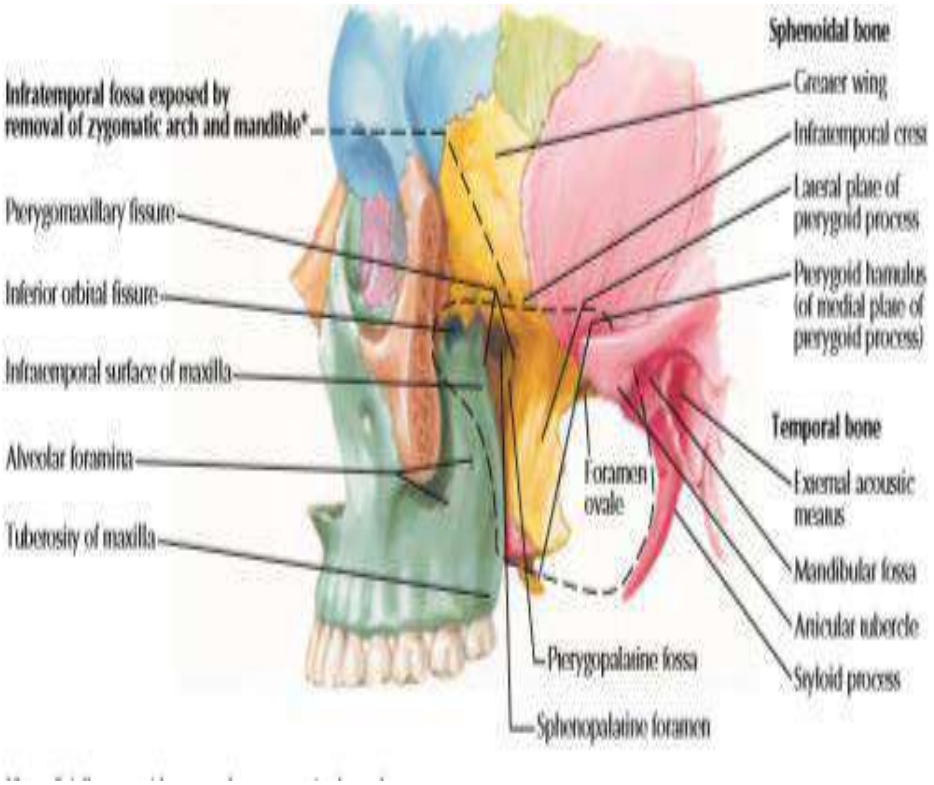
AXIAL SECTION OF ETHMOID SINUS[166]

Orbital encroachment occurs secondary to the ethmoid, maxillary sinuses,and the nasolacrimal duct involvement.The extension occurs by direct contiguous or hematogenous spread.The usual site of extension are the pterygomaxillary fissure, and hence inferiorly towards the palate and superiorly the orbit through the orbital fissure;The extension to the cavernous sinus and brain occurs via the orbital apex. Singh V et al.[169]

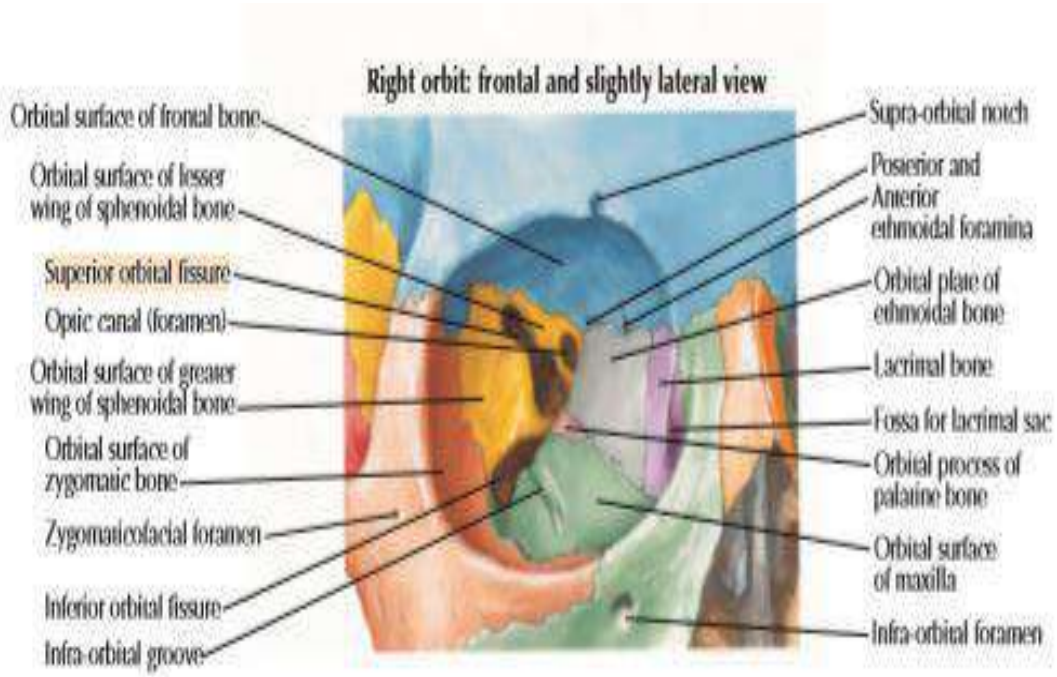
Hosseini *et al*. study on 10 patients concluded that the pterygopalatine fossa is a reservoir of the disease through which it can spread to the neighbouring structures, including the retroglobal space of the orbit and the infratemporal fossa.[165]



PTERYGOPALATINE FOSSA[166]

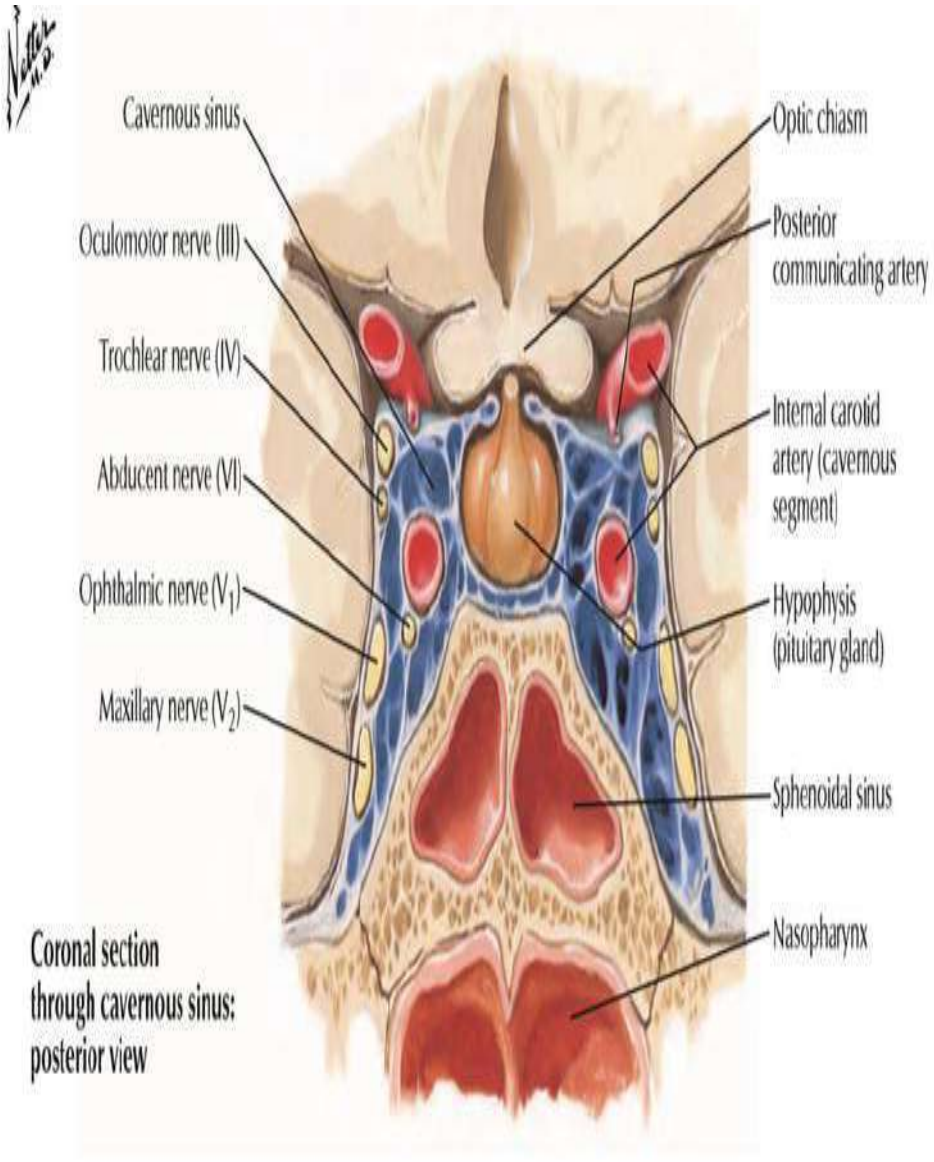


INFRATEMPORAL FOSSA[166]


Right orbit: frontal and slightly lateral view
Orbital surface of frontal bone
Supra-orbital notch
Orbital surface of lesser wing of sphenoidal bone
Posterior and Anterior ethmoidal foramina
Superior orbital fissure
Orbital plate of ethmoidal bone
Optic canal (foramen)
Orbital surface of greater wing of sphenoidal bone
Lacrimal bone
Fossa for lacrimal sac
Orbital surface of zygomatic bone
Orbital process of palatine bone
Zygomaticofacial foramen
Orbital surface of maxilla
Inferior orbital fissure
Infra-orbital groove
Infra-orbital foramen

RIGHT ORBIT: FRONTAL AND SLIGHTLY LATERAL VIEW[166]

The venous thrombosis in the pterygopalatine fossa and the inferior orbital fissure results in edema of the eyelids, conjunctival chemosis and proptosis; Ophthalmoplegia secondary to orbital infiltration through the superior orbital fissure, and infection at this juncture rapidly spreads to the retrobulbar space and the orbital apex.Optic nerve invasion and retinal artery thrombosis lead to irreversible loss of visual acuity, with potential thrombosis of the cavernous sinus. This warrants early treatment to limit intracranial extension.[165]

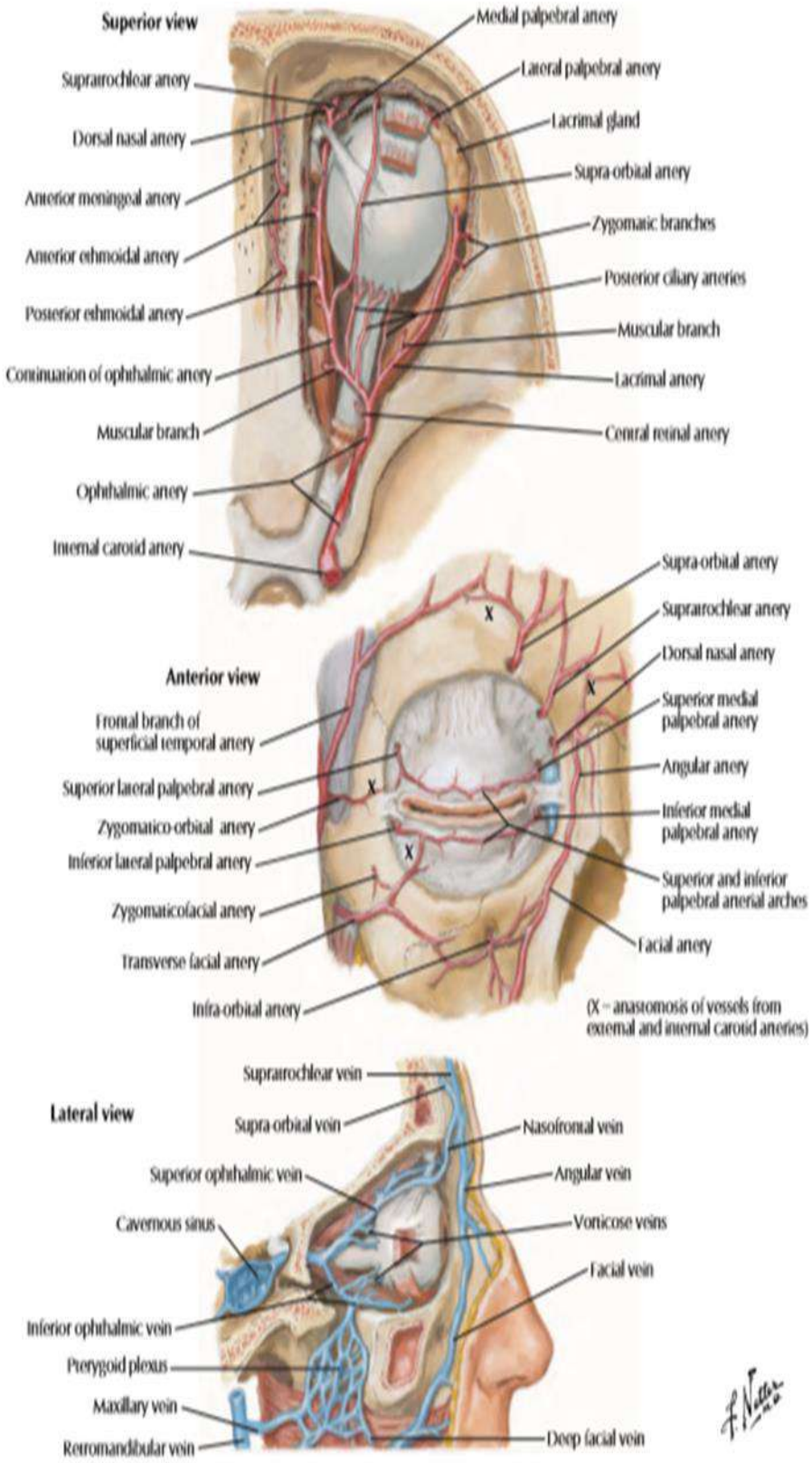


CORONAL SECTION THROUGH CAVERNOUS SINUS (POSTERIOR SPREAD FROM SPHENOID SINUS[166]

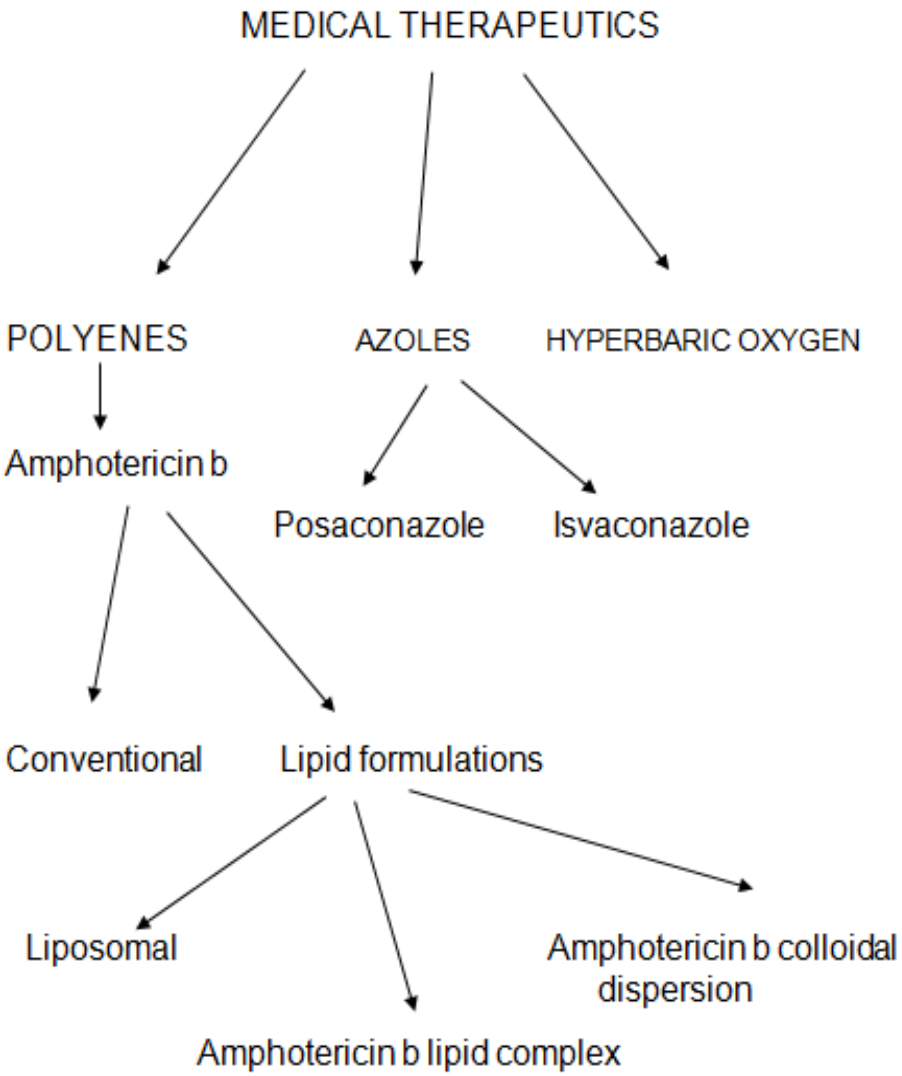
The fungus invades the cranium through either the orbital apex, cribriform plate or fovea ethmoidalis of the ethmoid bone or from superior orbital fissure by perineural route, lateral walls of sphenoid and ultimately proves fatal. Occasionally, cerebral vascular invasion can lead to hematogenous dissemination of the infection with or without development of mycotic aneurysms.Wali U et al 2012[170]

VASCULATURE OF THE ORBIT

The angioinvasive property of the fungus, facilitates invasion of the central retinal artery or the ophthalmic artery, with consequent central retinal artery occlusion (CRAO) or ophthalmic artery occlusions (OAO).[170]



ARTERIAL SUPPLY AND VENOUS DRAINAGE OF ORBIT[166]


MEDICAL THERAPEUTICS
POLYENES
AZOLES
HYPERBARIC OXYGEN
Amphotericin b
Posaconazole
Isvaconazole
Conventional
Lipid formulations
Liposomal
Amphotericin b colloidal dispersion
Amphotericin b lipid complex

MEDICAL THERAPEUTICS-

1. POLYENES

Intravenous amphotericin b is the drug of choice for mucormycosis.

Mechanism of action –

Amphotericin B binds with ergosterol, a component of the cell membrane of fungus, forming pores that permit rapid leakage of monovalent ions (K^+, Na^+, H^+ and Cl^-), causing oxidative stress and subsequent fungal cell death.[171]

Types of amphotericin b –

1. Conventional
2. Lipid formulations of amphotericin b

   Amphotericin B Colloidal Dispersion (ABCD) (Amphotec®)

   Amphotericin B Lipid Complex (ABLC) (Abelcet®)

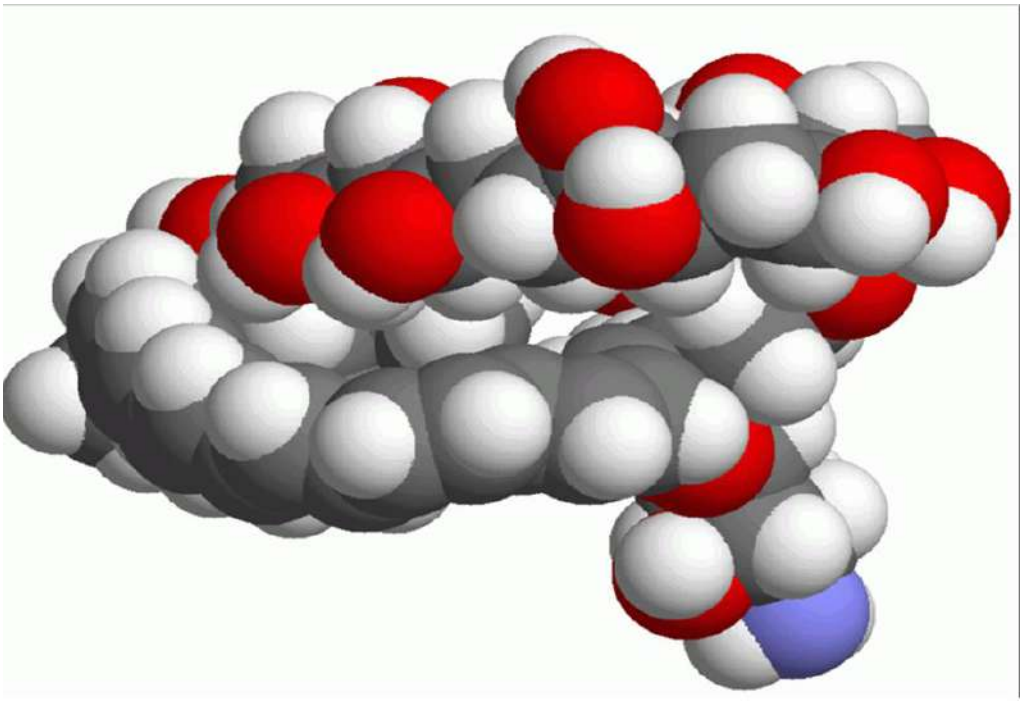
   Liposomal amphotericin B (AmB) (Ambisome

CONVENTIONAL AMPHOTERICIN B

PHARMACOKINETICS-

This original formulation of sodium deoxycholate has more solubility[172] and it binds extensively to plasma proteins,distributed through out the body, is administered intravenously.[173] Being the original formulation of amphotericin, it is captioned as "conventional" amphotericin.

DOSE – recommended 1-1.5 mg /kgbody weight /day[66]



SPACE FILLING MODEL OF AMPHOTERICIN B[176]

SIDE EFFECTS-

- RELATED TO TRANSFUSION–

Serious reactions after infusion (within 1 to 3 hours), consisting of high fever, shaking chills, hypotension, anorexia, nausea, vomiting ,dyspnea and tachypnea, headache drowsiness, with generalized weakness. The violent chills and fevers have been nicknamed "shake and bake"[174,175] Hartselscott et al 2016

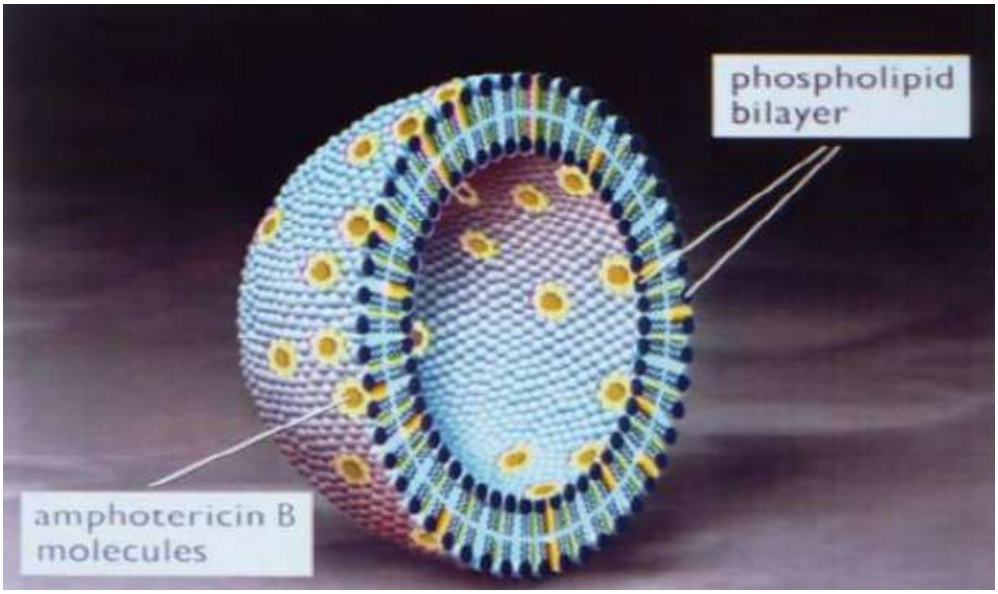
- NEPHROTOXICITY –

Vasoconstriction and direct interaction with the distal tubule cell membranes leads to a dose limiting nephrotoxicity. Conventional amphotericin B binds to the cholesterol in the cell membrane of the distal tubules with consequent loss of electrolytes, impaired urinary acidification, reduced concentration, and renal tubular acidosis. Persistent tubular damage eventually leads to a decrease in glomerular filtration rate (GFR) that further constricts the afferent arterioles.[176]

LIPOSOMAL AMPHOTERICIN B (L-AMB)

It is a liposomal formulation of Amphotericin B intercalated into the lipid bilayer and is a lyophilized sterile product for intravenous infusion

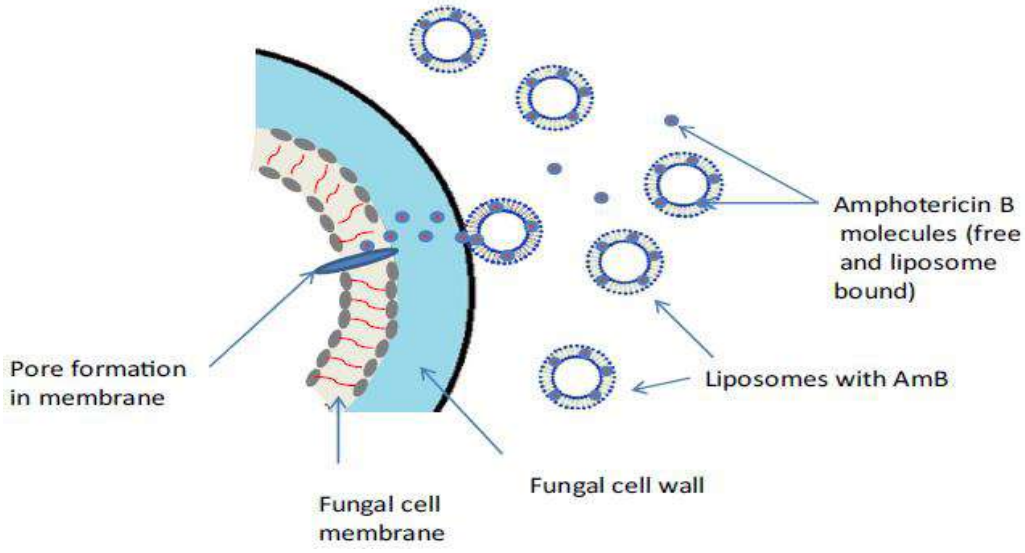
Liposomes (for drug delivery) are spherical vesicles characterized by an aqueous core surrounded by a lipid bilayer.[177]



CROSS SECTION VIEW OF LIPOSOME [177]

MECHANISM OF ACTION OF LIPOSOMAL AMPHOTERICIN B-[177]

- The liposome specifically used in LAmB is designed to enable parenteral administration and facilitate the stability of amphotericin B within the liposome
- Amphotericin B is retained within the liposome and on contact between the liposome and the fungus, disengages from the liposome to bind to the ergosterol in the membrane of fungus.
- This transfer of amphotericin B between the liposome and the fungus occurs most efficiently at the body temperature Adler-Moore JP et al 1993[177]


Amphotericin B molecules (free and liposome bound)
Pore formation in membrane
Liposomes with AmB
Fungal cell wall
Fungal cell membrane

MECHANISM OF ACTION OF LIPOSOMAL AMPHOTERICIN B[177]

L-AMB DOSAGE FOR TREATMENT OF MUCORMYCOSIS[177]

- ECMM/ESCMID (European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology Joint Clinical Guidelines) recommend the use of L-Amb with a daily dosage of at least 5 mg/kg/day for mucormycosisO. A. Cornely et al 2013.[66]

Dosages at 10 mg/kg/day are strongly supported by ECMM/ ESCMID for cerebral infections. Moreover, because of better diffusion, L-Amb should be favored in central nervous system infections.O. A. Cornely et al 2013.[66]

AMPHOTERICIN B LIPID COMPLEX

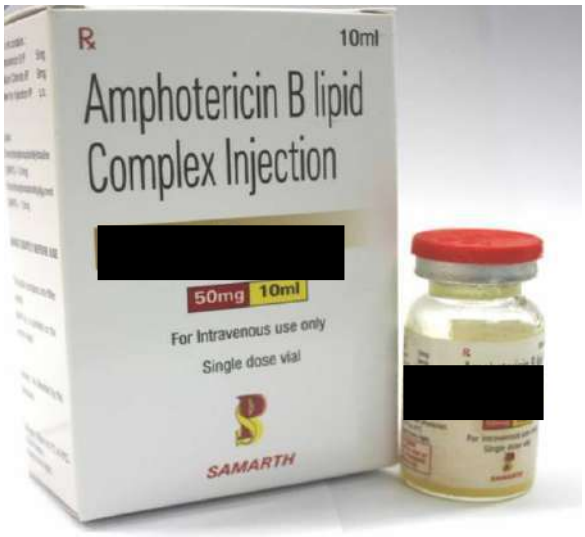
Amphotericin B Lipid Complex consists of AmB complexed with 2 phospholipids in a 1:1 drug to lipid molar ratio. The 2 phospholipids L-α-dimyristoylphosphatidyl choline (DMPC) and L-α-dimyristoyl phosphatidylglycerol (DMPG) are present in a 7:3 molar ratio Janoff et al 1993[178]Amphotericin B Lipid Complex is characterized by lipid stabilized AmB aggregates appearing as ribbon-like structures.

After iv administration,[178]Amphotericin B Lipid Complex is rapidly cleared from the blood, and high concentrations are sequestered in the reticuloendothelial tissues in the liver, spleen, and lung Adedoyin et al 1997.[179] At the infected tissue sites, AmB is thought to be selectively released from the lipid complex by the fungal lipases.

MECHANISM OF ACTION

- Amphotericin B lipid complex has a stronger affinity to ergosterol as compared to cholesterol (the component of human cell membrane)
- The drug phospholipids are broken down only by fungal phospholipases thus releasing AmB at the site of infection selectively
- By encasing amphotericin B to a lipid structure, the active drug becomes less available and less toxic to cholesterol containing human cell membranes.[180]

Amphotericin B lipid complex is US FDA approved for use as second-line therapy for the treatment of systemic fungal infections in patients who are refractory to or intolerant of conventional Amphotericin B or other systemic antifungal agents, have renal impairment or other contraindications to Amphotericin B, or have developed Amphotericin B nephrotoxicity.[180]



RECOMMENDED DOSE-

- For severe systemic infections treatment is generally recommended at 5.0 mg/kg for at least 14 days.
- Amphotericin B lipid complex is administered by intravenous infusion at a rate of 2.5 mg/kg/hr.

- An initial test dose of 1.0 mg is infused intravenously over 15 minutes. Mixed with 5% Dextrose Injection and administered as a 1mg/ml infusion mixture.[180]

United States food and drug administration (US FDA) approval for clinical use of were derived from 556 cases of invasive fungal infections collected through an open-label, single-patient, emergency-use study of patients who were refractory to or intolerant of antifungal therapy Walsh et al 1998.[181] During the course of Amphotericin B lipid complex therapy, serum creatinine levels significantly decreased from baseline (P < .02). Among 162 patients with serum creatinine values > or = 2.5 mg/dL at the start of Amphotericin B lipid complex therapy (baseline), the mean serum creatinine value decreased significantly from the first week through the sixth week (P < or = .0003). Among the 291 mycologically confirmed cases evaluable for therapeutic response, there was a complete or partial response to ABLC in 167 (57%), including 42% (55) of 130 cases of aspergillosis, 67% (28) of 42 cases of disseminated candidiasis, 71% (17) of 24 cases of zygomycosis, and 82% (9) of 11 cases of fusariosis.

AMPHOTERICIN B COLLOIDAL DISPERSION

Amphotericin B colloidal dispersion (ABCD) is a near 1:1 discoidal complex of amphotericin B (AMB) and sodium cholesteryl sulphate (SCS) arranged as a bilayer of sodium cholesteryl sulfate interspersed with Amphotericin B via noncovalent interactions.[182]

The data in the British literature on treatment of zygomycosis with Amphotericin B colloidal dispersion is limited. The first detailed clinical description of the treatment of zygomycosis with Amphotericin B colloidal dispersion is by Moses *et al.*1998.[182] In this study, three patients with life-threatening rhinocerebral zygomycosis were treated with Amphotericin B colloidal dispersion. All patients had high serum creatinine levels as a result of prior treatment with Amphotericin B; these levels reverted to normal during treatment with Amphotericin B colloidal dispersion. Two patients with diabetes mellitus were cured after receiving a combination of surgery and Amphotericin B colloidal dispersion therapy. The third patient, who had myelodysplastic

syndrome, had an initial good response with cure of the fungal infection; however, he eventually died of his primary illness. In a review by Noskin G et al[183] 1999 of 21 patients with invasive zygomycosis treated with Amphotericin B colloidal dispersion from five phase I and phase II studies, 12 of 20 (60%) patients responded. These patients, all of whom had undergone bone marrow or organ transplantation, or had haematological malignancies or diabetes, were given Amphotericin B colloidal dispersion on the basis of pre-existing renal insufficiency, development of nephrotoxicity during Amphotericin B therapy, or fungal infection that failed to respond to Amphotericin B therapy combined with surgical debridement. Infection was disseminated in six patients and localized to the sinuses, lower respiratory tract or skin in the other patients. Amphotericin B colloidal dispersion was given at a mean dose of 4.8 mg/kg per infusion for a mean duration of 37 days.

Gleissner et al 2004 study [184] described 2 cases of successfully treated rhino-cerebral zygomycosis and gave an overview of 120 patients from the literature with underlying hematological or oncological disorders. This documented the improved survival in sinus (15/17 patients surviving) and cutaneous (6/9 patients surviving) disease. Hematological patients with pulmonary (9/30 patients surviving) or disseminated (4/38 patients surviving) zygomycosis still have a poor prognosis. The clinical course of sinus-orbital involvement (4/11 patients surviving) follows sinus-cerebral (2/3 patients surviving) or cerebral (3/6 patients surviving) disease. Besides deoxycholate amphotericin B (AmB) (24/62 patients surviving), patients seemed to benefit from liposomal amphotericin B (L-AmB) (10/16 patients surviving) or sequential Amphotericin B / L-Amphotericin B treatment (6/8 patients surviving). Alternative treatment options led only in a few patients to success. Furthermore, treatment of mucormycosis with liposomal amphotericin B (LAmB) was associated with a 67% survival rate, compared to 39% survival when patients were treated with Amphotericin B ($p = 0.02$)

Reed c et al[185] study described the forty-one patients with biopsy-proven ROCM were identified over 12 years; 23 (56%) of these

patients were Hispanic, and 34 (83%) were diabetic. Patients treated with polyene-caspofungin therapy (6 evaluable patients) had superior success (100% vs. 45%; Pp.02) and Kaplan-Meier survival time (Pp.02), compared with patients treated with polyene monotherapy. Patients treated with amphotericin B lipid complex had inferior success (37% vs. 72%; Pp.03) and a higher clinical failure rate (45% vs. 21%; Pp.04), compared with patients who received other polyenes. However, patients treated with amphotericin B lipid complex plus caspofungin had superior success (100% vs. 20%; Pp.009) and survival time (Pp.01), compared with patients who received amphotericin B lipid complex alone. The benefit of combination therapy, compared with monotherapy, was most pronounced in patients with cerebral involvement (success rate, 100% vs. 25%; Pp.01). In multivariate analysis, only receipt of combination therapy was significantly associated with improved outcomes (odds ratio, 10.9; 95% confidence interval, 1.3-;Pp.02).

TRIAZOLES –

POSACONAZOLE –

MECHANISM OF ACTION –

It inhibits C-14 alpha demethylase (a cytochrome p 450 enzyme) blocking the demethylation of lanosterol to ergosterol – the principal sterol of fungal membranes, thus inhibiting fungal cell growth.

Most common side effects include gastrointestinal discomfort and headache.

RECOMMENDED DOSE –

ESCMID AND ECMM(European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology Joint Clinical Guidelines) (O. A. Cornely et al 2013)[66] joint clinical guidelines for treatment of mucormycosis recommend posaconazole as salvage therapy in the dose of 200 mg 4 times a day for zygomycosis refractory or intolerant to the other therapy.

Posaconazole was often utilized late in the disease progression when patient had already received the maximum recommended dosage of Amphotericin b and had extensive surgical debridement.

Rai et al highlights a case series of rhinomaxillary mucormycosis in immunocompetent patients diagnosed and managed successfully with surgical debridement and oral Posaconazole administration on out-patient basis.[186]

The efficacy of posaconazole as a treatment option is further called into question by reports of mucormycosis developing as a breakthrough infection while on posaconazole prophylaxis.[187–189] Thus, posaconazole cannot be recommended as a first-line treatment for mucormycosis.

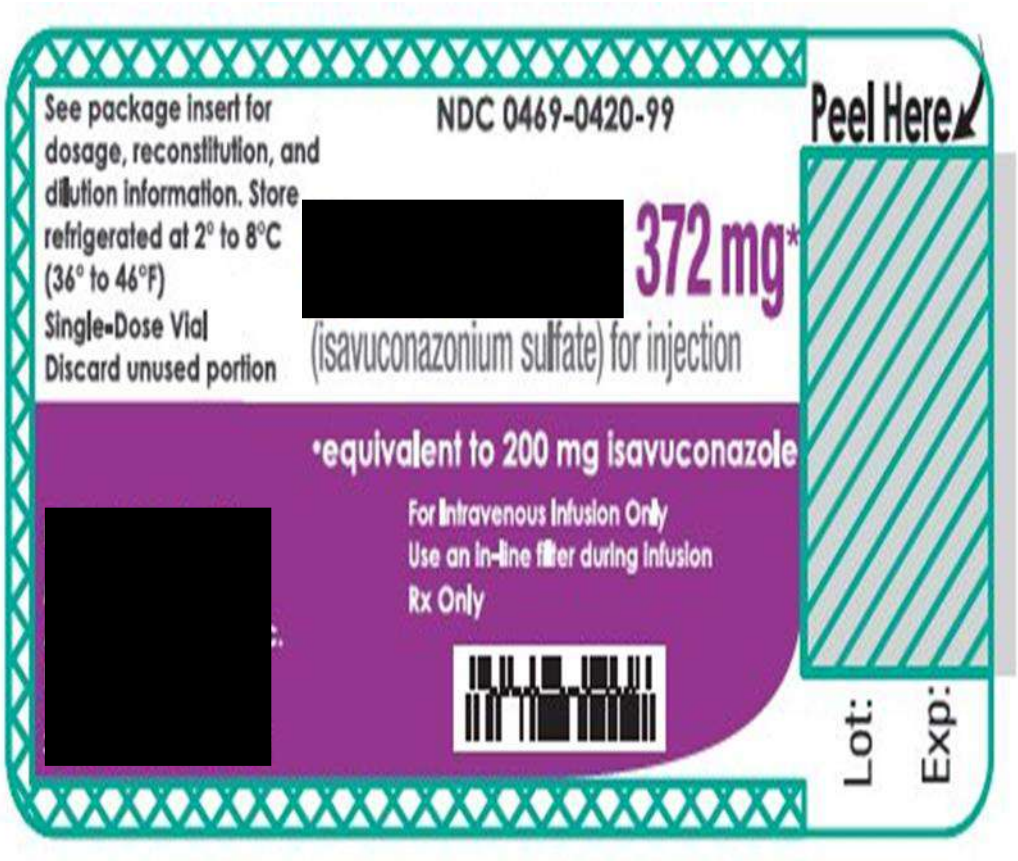
In contrast, van Burik et al. [190] reported 60% response rates (45% partial response, 15% complete response) for salvage therapy in patients with mucormycosis who were refractory to or intolerant of

polyenes. Greenberg et al.[191] reported similar results. Hence, posaconazole is an option for salvage therapy for these infections.

ISVUCONAZOLE

Mechanism of action-

The triazoles, including isavuconazole, exert their effects within the fungal cell membrane. The inhibition of cytochrome P450 (CYP)-dependent 14-α-demethylase by azoles prevents the conversion of lanosterol to ergosterol. This mechanism results in the accumulation of toxic methyl sterols and resultant inhibition of fungal cell growth and replication. The side arm of the active isavuconazole molecule allows for greater affinity of isavuconazole for the binding pocket in the fungal CYP51 protein increasing the antifungal spectrum and conferring activity against some isolates resistant to other triazoles.[192]


See package insert for dosage, reconstitution, and dilution information. Store refrigerated at 2° to 8°C (36° to 46°F)
Single-Dose Vial
Discard unused portion
NDC 0469-0420-99
372 mg*
(isavuconazonium sulfate) for injection
*equivalent to 200 mg isavuconazole
For Intravenous Infusion Only
Use an in-line filter during infusion
Rx Only
Peel Here
Lot:
Exp:

RECOMMENDED DOSE- Administered with a loading dose of 372 mg/200mg three times a day for two days and 372 mg/200mg daily thereafter.[66]

The VITAL study was a Phase III, open-label, noncomparative trial evaluating the efficacy and safety of isavuconazole in patients with

invasive aspergillosis with renal impairment or as primary or salvage treatment for mucormycosis. Isavuconazole 200 mg (IV or oral) was given three times daily for six doses, followed by 200 mg/day until invasive fungal disease resolution or ≥180 days. Outcomes included mortality at day 42 and overall response as determined by an independent DRC. Of the 149 patients enrolled, 37 had proven (86%) or probable (14%) invasive mucormycosis by European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria. Mortality at day 42 was 37.8%. A matched case-control cohort of 33 patients treated with amphotericin B from the FungiScope registry was compared with 21 patients who received isavuconazole for the primary treatment of mucormycosis. Mortality rates were not significantly different between cases and controls (33.3% and 41.3%, respectively). A relationship between trough isavuconazole levels, fungal isolate MICs, and key outcomes could not be identified, possibly due to the relatively small number of patients with data available. Clinical responses occurred across the range of isavuconazole MICs and trough levels observed. The FDA has licensed isavuconazole for the treatment of mucormycosis, while the EMA has licensed isavuconazole in those for whom amphotericin B formulations are inappropriate. This difference suggests the continued opinion that amphotericin B formulations are first-line therapy for most cases of mucormycosis.[193]

Risk of break through mucormycosis has been reported with isvuconazole.[193]

HYPERBARIC OXYGEN

Hyperbaric oxygen therapy has been proposed as an adjunctive therapy.

MECHANISM OF ACTION –

The proposed mechanism is that an increase of free oxygen radicals stimulates the oxygen-dependent peroxidase system, thereby enabling leukocytes to kill microorganisms. Case reports discuss benefits but the role of hyperbaric oxygen is not yet known.[66]

SURGICAL THERAPEUTICS -

AIM-

- Thrombosis of blood vessels and consequent tissue necrosis results in poor penetration of antifungal medication at the site of infection and thereby debridement of necrotic tissue is critical as it facilitates adequate drug delivery to the site of involvement. Spellberg B, Ibrahim A 2010
- Early and an aggressive surgical debridement is crucial for successful management of the invasive fungal disease. This can be undertaken intranasally endoscopically or through the conventional open approach. The aim is to remove the maximal necrotic tissue. The fungal infested tissues rarely bleed, so debridement is carried out until normal, well-perfused, bleeding tissue is encountered. Regular repeat debridement may be needed until clinical improvement and revitalised bleeding tissue is established. With extensive spread of the disease, orbital exenteration, along with removal of the sinuses, its mucosa and necrotic bone may be required. Spellberg B, Ibrahim A 2010[194]

Surgery is essential for favourable outcome in patients with mucormycosis Roden et al [5] Subjects who do not undergo surgical intervention inmucormycosis have a far higher mortality rate than patients who do so.Nithyanandam S, Jacob MS, Battu RR, et al 2003,[77] Peterson KL, Wang M 1997,[75] Khor BS et al 2003,[76] Petrikkos G, Skiada A, Sambatakou H, et al 2003.[79]

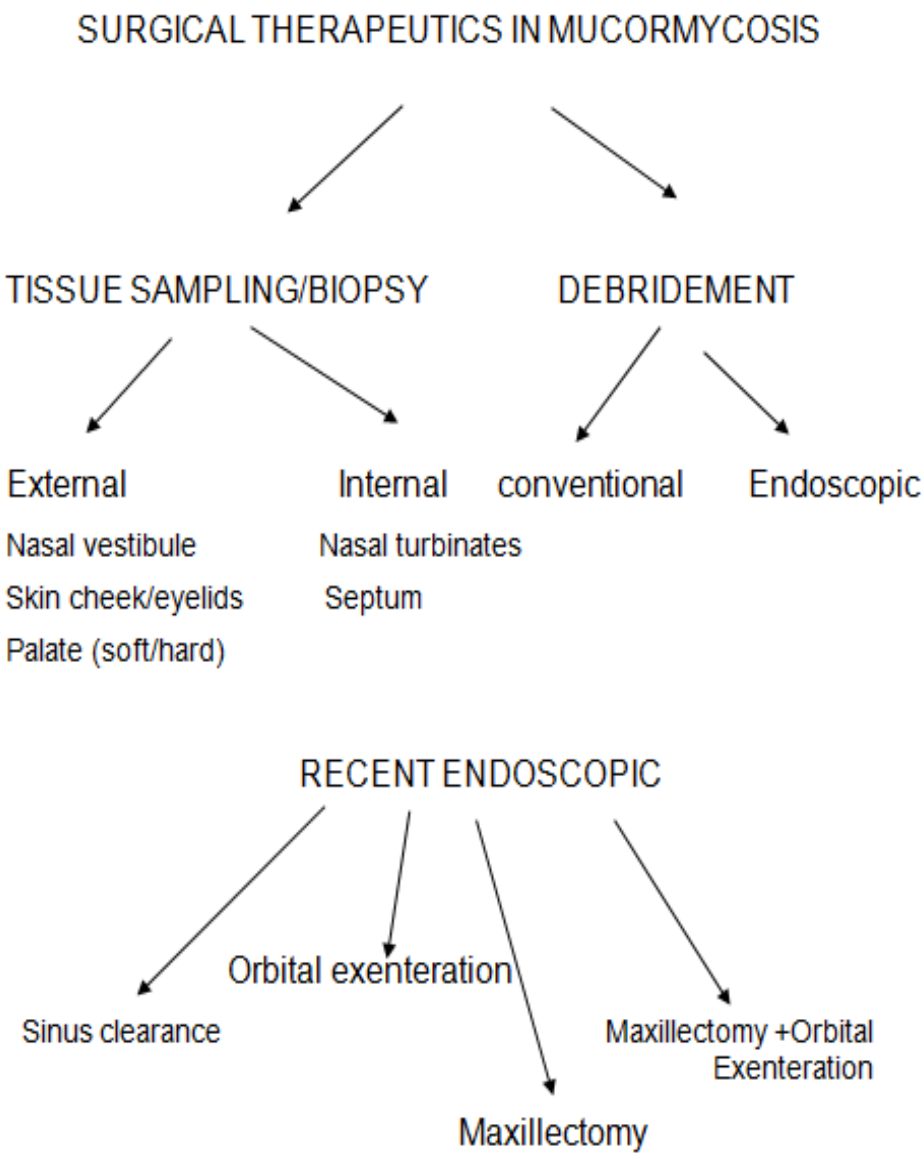
A multivariate analysis from an European Federation of Medical Mycology (ECMM) case registry Skiada, L Pagano, A Groll, et al 2011[47] and a retrospective analysis of a national case series found surgery associated with survival F Lanternier, E Dannaoui, G Morizot, *et al.*2012.[195] Surgery is crucial in rhino-orbito-cerebral infection, as evidenced in retrospective study, where the impact of local control on survival is striking P Vironneau, B Verillaud, H Tran, et al.2013[196]

Surgery is easy and takes less time as it requires an almost bloodless field.

Intraoperative frozen sections delineate the margins of infected tissues so that uninvolved tissues can be spared from debridement Reed C, Bryant R, Ibrahim AS, et al.[185]

The extent and timing of surgical debridement necessary to maximize outcomes of mucormycosis has not been defined. Spellberg et al 2010.[194]

Aggressive and early surgical debridement is vital to successful treatment of mucormycosis. This involves resection of involved tissues of skin, muscle, bone, face, nose, sinuses, orbit, temporal and infratemporal region Rapidis AD 2009.[197]


SURGICAL THERAPEUTICS IN MUCORMYCOSIS
TISSUE SAMPLING/BIOPSY
DEBRIDEMENT
External
Internal
conventional
Endoscopic
Nasal vestibule
Skin cheek/eyelids
Palate (soft/hard)
Nasal turbinates
Septum
RECENT ENDOSCOPIC
Sinus clearance
Orbital exenteration
Maxillectomy
Maxillectomy +Orbital Exenteration

SURGICAL INTERVENTION IN MUCORMYCOSIS INCLUDE–

I)TISSUE SAMPLING/BIOPSY

A)EXTERNAL FROM

i)nasal vestibule

ii) skin cheek/eyelids

iii)palate (soft/hard)

B) INTERNAL FROM

i) Nasal turbinates

- Inferior
- Middle

ii)Septum

II) DEBRIDEMENT

CONVENTIONAL NON ENDOSCOPIC

-intranasal approach

-external approach

RECENT ENDOSCOPIC

III) DEBRIDEMENT OF SINUSES

IV)ORBITAL EXENTERATION

V) MAXILLECTOMY

- MEDIAL

-INFERIOR

-TOTAL

-EXTENDED

VI) MAXILLECTOMY + ORBITAL EXENTERATION

Aggressive surgical debridement has been the classic treatment for rhinocerebralmucormycosis.The surgeon needs to debride the affected structures extensively, and restore the drainage of the sinuses.

Traditionally, various external or transantral procedures such as external ethmoidectomy or Caldwell-Luc's operation have been used, depending on the extent of invasion. Since the ethmoid sinus, sphenoid sinus, and maxillary sinus (in order of involvement) are the most

commonly affected craniofacial structures, it is feasible to use Endoscopic sinus surgery to debride the diseased tissue in most cases completely, especially early ones.[197]

Endoscopic sinus surgery was performed in nine patients. In six patients, Endoscopic sinus surgery was the only surgical procedure used. Of the remainingthree patients, two patients received ESS combined with Caldwell-Luc's operation, and the third received ESS together with Denker's operation.Roang san jiang Chen yihsu 1999.[198]

In more advanced cases in which the lesion cannot be completely debrided by Endoscopic sinus surgeries, traditional surgical procedures need to be added to remove the lesion completely.Roang san jiang chenyihsu1999.[198]

Moreover, the improved visibility in Endoscopic sinus surgeries as compared with traditional procedures may enable us to remove the lesion completely but spare the normal tissue. Therefore, wound healing can be accelerated.

Being a minimally invasive procedure, it can help even severely ill patients suffer less operative morbidity.

Because the application of Endoscopic sinus surgery is limited to the boundaries of the surgeon's field of vision, good preoperative staging of the extent of disease is mandatory. Preoperatively, the patient should be evaluated clinically to decide whether the maxillary sinus and hard palate are involved. If involved, the traditionally open surgeries need to be used to debride the lesion.

Endoscopic examination permits an accurate evaluation and appropriate planning of surgical intervention.

The computed tomography (CT) provides most accurate delineation of the lesion, in addition to early detection of rhinocerebral mucormycosis. It can depict whether the disease extends into the infratemporal fossa and pterygomaxillary fissure. If involvement of orbit is suspected, Computed tomography and magnetic resonance imaging scan should be used to delineate the extent of orbital lesion with respect to muscle and bone involvement.[138]

Depending on the extent of necrotic mucosa debridement steps include-[199]

1.Inferior turbinectomy

2.Middle turbinectomy

3.Partial septectomy or posterior septectomy

Debridement is combined with endoscopic sinus clearance.

STEPS IN ENDOSCOPIC SINUS SURGERY [199]

1. Patient positioning

2. Diagnostic nasal endoscopy to look for characteristic ischaemic and necrotic nasal mucosa and to delineate the extent of disease.

3. Topical anesthetic injections with 2% lidocaine in 1:100000 adrenaline.

4. Medialization of the middle turbinate to expose the osteomeatal complex (basal lamella relaxing incision is optional)

5. Uncinectomy with a zero-degree endoscope

6. Maxillary antrostomy: use a 30- or 45-degree endoscope to identify the maxillary sinus ostium, identify the floor of the orbit, and then follow it up to the medial orbital wall (lamina papyracea)

7. Removal of the ethmoid bulla; identification of the lamina papyracea in its medial wall

8. Identification of the basal lamella of the middle turbinate in the horizontal and oblique segments

9. Removal of the inferomedial part of the vertical middle turbinate basal lamella to penetrate into the posterior ethmoid sinus

10. Ethmoidectomy; stay low, between the superior turbinate medially and the lamina papyracea laterally

11. Identification of the sphenoid face

12. Identification of the posterior skull base, either in the posterior ethmoid (possible in the absence of polyps or in a single tier of cells) or following the sphenoid face up to the skull base

13. Clearance of skull base in a posterior to anterior direction, removing ethmoid partition

14. Sphenoid sinusotomy (if needed) through the medial inferior triangle of the posterior ethmoid box or by identifying it in the sphenoethmoidal recess

15. Identification of the frontal recesses, frontal sinusotomy

16. Medialization of the medial middle turbinate by creating adhesion between medial surface and septum (suture or pack)

17. Placement of a middle meatal spacer.

Hosseini and Borghei concluded that the pterygopalatine fossa is invariably involved in the spread of the infection and may actually serve as a reservoir of disease, leading to recurrence despite adequate surgical debridement.[165]

The facial soft tissues, palate and infratemporal fossa can be infected through connecting pathways from the pterygo-palatine fossa; therefore, debridement of the pterygopalatine fossa seems to be the definitive method of managing this infection.[165]

Pterygopalatine fossa can be approached by gaining access through endoscopic medial maxillectomy approach and conventional external maxillectomy approaches.[197]

ENDOSCOPIC MEDIAL MAXILLECTOMY – [200]

It is performed to gain access to the anterior wall of maxillary sinus, pterygopalatine fossa and infra temporal fossa.

The maxillary anrtrum is enlarged posteriorly upto posterior wall of maxillary sinus.

A sharp osteotome is used to cut the bone at junction of medial maxillary wall and nasal floor.

A posterior vertical cut needs to enter maxillary sinus adjacent to posterior wall of maxillary sinus and into large antrostomy.

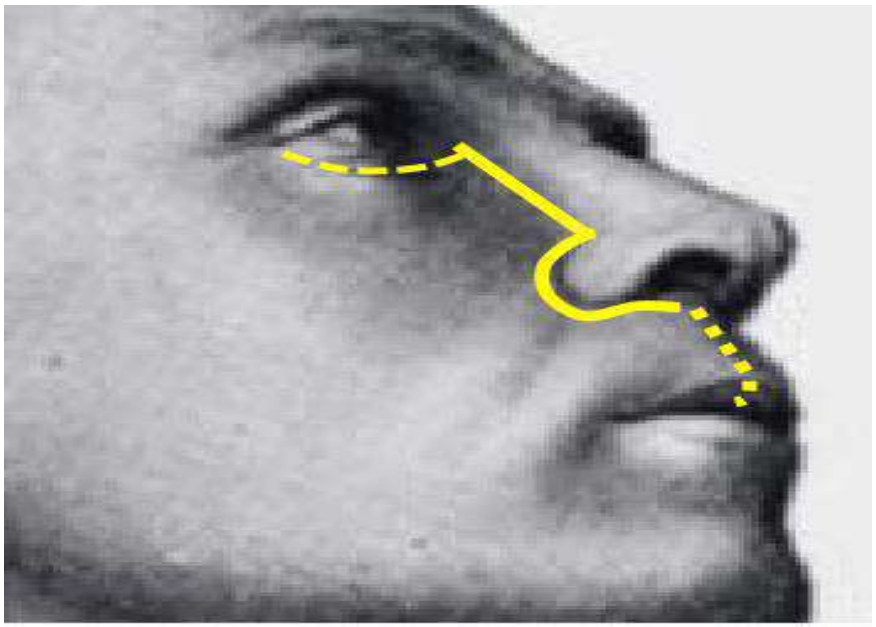
ACCESS TO PTERYGOPALATINE FOSSA AND INFRATEMPORAL FOSSA[200]

The posterior and lateral wall of maxillary sinus is removed to access pterygopalatine fossa.

Bone removal can continue until anterior wall of maxillary sinus is reached by using the hajek -koeffler punch or thorough bakebiting Blakesley foreceps.

CONVENTIONAL TOTAL MAXILLECTOMY [201]

Total maxillectomy may be done externally via lateral rhinotomy, midfacial degloving or Weber Ferguson approach.



LATERAL RHINOTOMY INCISION [201]

The midfacial degloving approach avoids facial scars and is suited to resections that do not extend above the orbital floor i.e. do not include resection of the lamina papyracea and ethmoids. Once the resection requires removal of the medial wall of the orbit and the ethmoids, lateral rhinotomy provides better access.[201]

EXTENDED TOTAL MAXILLECTOMY RESECTIONS

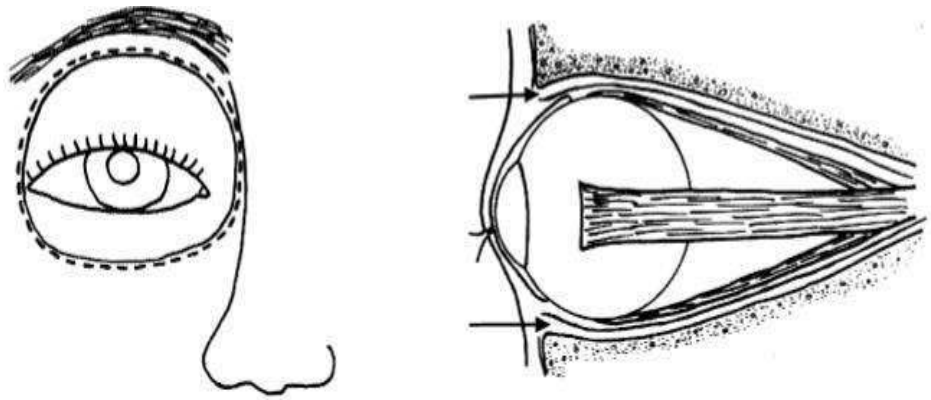
Total maxillectomy may be extended to include the malar complex, sphenoid sinus, cribriform plate (craniofacial resection), contralateral maxilla, skin, or orbit. When resection extends to the contralateral maxilla, then an osseocutaneous free flap reconstruction is imperative.[201]

ORBITAL EXENTERATION

The entire orbital contents down to the bone are removed in this mutilating surgery.

The most critical decision in the management of rhino-orbital mucormycosis is whether the orbit should be exenterated. The literature fails to provide a broad base of information of how physicians determine the need for exenteration in daily practice. The decision for

exenteration often depends on the judgment of the treating otolaryngologist. The authors report their experience and outline that orbital exenteration may not be mandatory in all cases of rhino-orbital mucormycosis.[201]



ORBITAL EXENTERATION SKIN INCISION AND PLANE OF DISSECTION BETWEEN THE ORBITAL BONE AND THE PERIOSTEUM [201]

In 1988 Ochi JW et al reported 11 patients with rhinocerebral mucormycosis over past 6 years, out of which seven patients underwent aggressive surgical debridement; all seven had disease involving the sphenoethmoidal complex, requiring external ethmoidectomy with or without sphenoidotomy. Six patients had maxillary sinus disease, requiring Caldwell-Luc antrostomy or maxillectomy. Three patients required orbital exenteration.and mortality of 82%.[202]

The Dr. Manuel Gea González General Hospital study[164] on rhino-orbital mucormycosis, where the pterygomaxillary fossa was systematically surgically approached and orbital exenteration is performed or not based on the spreading of the infection to the orbital apex or the orbital fissure, with a historical group where these criteria were not applied. Fifteen cases were included, eight in historic group A (treated within the period encompassed from January 2008 to December 2012) (and seven in the study group B within the period encompassed from January 2013 to December 2014). Medical treatment was provided with control of the underlying disease

(amphotericin B and low molecular weight heparin) as well as surgical treatment with extensive debridement including endoscopic ethmoidectomy and exploration of the pterygomaxillary fossa, also performing orbital exenteration only in patients who presented orbital apex syndrome in group B. In group A, there was a mortality rate of 50%, in group B all patients were clinical cured; however, the two patients with hematologic diseases died of complications not related to the fungal infection.[164]

Chetchotisakd P et al 1991 Thailand study reported 11 patients with rhinocerebral mucormycosis who underwent surgical treatments (extensive debridement, 8 cases; sphenoidectomy, 7 cases; ethmoidectomy 8 cases; maxillectomy 5 cases and orbital exenteration, 6 cases). Amphotericin B was administered to all patients as soon as the diagnosis of RCM was made. Only three patients survived.[203]

In a study by Musharaf. Baig et al in 2007 on 10 patients with rhinocerebral mucormycosis Surgical intervention included ethmoidectomy, sphenoidectomy, partial or radical maxillectomy and debridement of the cheek soft tissue and pterygopalatine fossa with or without orbital exenteration. The most frequent approach for debridement was sublabial facial degloving. Six patients died due to various causes, one lost to follow up, three were alive and disease free (1 to 5 years).[204]

Restrospective review of cases of rhinocerebral mucormycosis by Soumya MS et al 2014 over period of 10 years documented surgical intervention as Out of 60 patients 38 underwent debridement. 10 underwent orbital exenteration and 12 received periorbital ampho injection.[205]

PROGNOSTIC INDICATORS IN MUCORMYCOSIS

The underlying illness, the time between the onset of the disease and the establishment of treatment, and the occurrence of cerebral ischemic events play a role in worse survival rates. Factors favouring rapid recovery in patients were early diagnosis and prompt commencement of treatment. Soumya MS et al 2014[205]

Yohai et al 1994 in their extensive case study and literature review, reported the survival in patients with diabetes to be 77% as compared to only 34% in nondiabetics (otherwise immuno-compromised). The better survival in diabetics is perhaps due to better capabilities of present therapeutic regimens to check hyperglycemia and ketoacidosis, which is very important in prognosis of diabetics with rhino-orbito-cerebral mucormycosis.[150]

According to Ferry et al 1990 delay in diagnosis and treatment is a bad prognosticator in this condition, and patients in our settings usually present to a tertiary care facility such as ours, only when the disease is quite extensive.[155]

Lehrer et al 1993,[206]have also found that the patients most likely to survive are those who are diabetics and have localized mucormycosis infection in the head and neck region. This also adds strength to our hypothesis that delay in presentation was responsible for the relatively lower frequency of survival.

Literature review of 113 articles (1943 to 2004) at The Hamilton Eye Institute, University of Tennessee Health Science Center, USA, parameter estimates (PE <or= 1.00) indicated that patients with mucormycosis with following parameters are less likely to survive compared with patients without these conditions- [207]

- age >46 years,
- frontal sinus involvement,
- Fever

Patients treated with amphotericin B (OR, 4.476) and those with diabetes (OR, 4.987) are more likely to survive compared with patients without these conditions. Exenterated patients with fever were more likely to survive compared with nonexenterated patients with fever (P=0.0468)

Bhansali et al study 2004 predictors for survival in retrospective, non-comparative, interventional in 35 patients with Rhino-orbito-cerebral mucormycosis included[156]

- Lag time between the first symptom referable to mucormycosis and
- Treatment with amphotericin B (lag time between 3–9 days *v* 10–45 days, survival 85% *v* 55%, $p<0.05$),
- Facial and lid gangrene (33% *v* 71%, $p<0.05$)
- Hemiplegia (50% *v* 72% $p<0.05$), and
- The cerebral invasion by mucorale (50% *v* 72%, $p<0.05$).

Those with loss of vision, ophthalmoplegia, palatal necrosis, and altered sensorium at presentation too had a poor survival ($p<0.05$). However, diabetic ketoacidosis did not affect the survival outcome ($p>0.05$). Those who received surgical treatment in addition to amphotericin B had a better survival than who received amphotericin B alone.[156]

Global Literature on sinonasal mucormycosis with medical, surgical treatment and outcome-

Sr. No	STUDY GROUP	SUBJECTS	ASSOCIATED COMORBIDITY	TREATMENT	SURVIVAL
I	Reed et al [185] 1994-2006	41	Diabetes Mellitus	AMPHO-B or ampho-b = caspufungin	14/34(41%)with ampho b monotherapy 6/7(86%) with combination therapy with caspufungin
II	Bhansali et al [156] 1990-2002	35	Diabetes Mellitus	Ampho-b with surgical debridement in 26/35	21/35(60%)
III	Rangel et al[37]	22	Diabetes Mellitus	Ampho-b +debridement	15/22(68%)
IV	Suslu et al[208] 2009	19	Haematological neoplasm	Ampho-b + debridement(13/19)or ampho-b without surgery (6/19)	Medical therapy with surgery 6/13(46%) No surgery 0/6(0%)
5	Bala et al[80] 2014	17	Diabetes Mellitus	Liposomal ampho-b +debridement	15/17(88%)
6	Nithyanamdam et al[77] 2003	16	Diabetes Mellitus	Ampho-b(0.7mg/kg/day)+intraorbitalampho-b +group A nasal sinus debridement and group B (nasal sinus debridement +orbital exenteration	Group A 7/7(100%) Group b 1/7(11%) Total (50%)

7	Prado et al[164] 2016	15	Diabetes Mellitus	Amphotericin b +ampho-b irrigation surgical debridement according to extent with or without exenteration with maxillectomy or pterygomaxillary exploration	Group A 4/8(50%) Group b 7/7 (100%)
8	Sun et al[209] 2010	11	Solid organ transplant	Ampho-b(conventional or liposomal)+ debridement	7/11(63.6)
9	Pagano et al[49] 2004	10	Haematological malignancy	Ampho-b +debridement (4/6)	6/10 (60%)
10	Shpitezer et al[210] 1995	10	Diabetes Mellitus	Ampho-b +debridement	2/10(20%)
11	Guevara et al[211] 2004	9	Diabetes Mellitus	Ampho-b +external or endoscopic debridement	5/9(55.9%)
12	Ghafur et al[212] 2013	9	Diabetes Mellitus	Ampho-b + surgical debridement	7/9(77.7%)
13	Kohn& helper[213] 1985	8	Diabetes Mellitus	Ampho-b with surgical debridement (without orbital exenteration) with ampho-b irrigations	8/8(100%)
14	Talmi et al[214] 2002	8	Haematological and other	Ampho-b (0.5-	5/8(62.5%)

			neoplasm	1.5mg/kg)+ debridement	
15	Gorjon et al[215] 2010	7	Haematological malignancy +DM	Ampho-b +debridement	2/7(28.5%)
16	Charfi et al[216] 2008	7	Diabetes Mellitus	Ampho-b +debridement	5/7(71.4)
17	Bhadada et al[217] 2005	6	Diabetes Mellitus	Ampho-b +debridement (5/6)	4/6(66.6%)
18	Sachdeva[218] 2013	6	Diabetes Mellitus	Ampho-b +debridement (4/6)	4/6(66.6%)
19	Arda et al[219] 2011	6	Haematological malignancy	Ampho-b +debridement	4/6(66.6%)
20	Alobid et al[220] 2002	5	Diabetes Mellitus	Ampho-b +debridement with exenteration (2/5) or endoscopic surgery (3/5)	5/5(100%)
21	Toumi et al[221] 2012	5	Diabetes Mellitus	Ampho-b (5/5)+ debridement (4/5)	2/5(40%)

MATERIALS AND METHODS

Source of Data

In this prospective clinical study the patients admitted with microbiologically/histopathologically proven sinonasal mucormycosis over a period of 1 year (January 2018 to December 2018) undergoing surgical and medical intervention at the department of ENT and Head & Neck surgery Dayanand Medical College & Hospital Ludhiana were studied.

METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA

Patients presenting in ENT head and neck services over a period of 1 year (January 2018 to December 2018) and were histopathologically and microbiologically detected to be Sinonasal mucormycosis, were included in the study.

Enrolled patients comprised of both immunocompromised and immunocompetent individuals.

Study was conducted regardless of age and gender. Patients were followed up after one, three and six months.

EXCLUSION CRITERIA

1. Patients proven with bacterial and fungal sinusitis other than mucormycosis

Data used:

1. History of the patient:

   The case histories of the patients with mucormycosis were analyzed prospectively regarding site of involvement, underlying disease, biochemical and haematological investigations, clinical course, mode of diagnosis, agents isolated, treatment instituted, and outcome of disease.

2. Clinical examination:

   General physical examination, Ear Nose Throat examination, complete ophthalmological examination and cranial nerve iii, iv, vi, viith nerve examination and nasal endoscopic examination was carried out.

3. Radiological assessment:

   Computed tomography and magnetic resonance imaging was undertaken to evaluate the extent of disease

4. Microbiological examination: KOH smear and fungal culture.

   Nasal specimen- nasal secretions, nasal mucosa, crusts, nasal scrapings, excised nasal polyp/tissue biopsy were collected and transported in saline in a sterile ,screw shaped container

   KOH MOUNT-for nasal secretions/scrapings 10-20% KOH and for biopsies 40% KOH was used.

   Slide KOH method:

   The sample was placed on a clean glass slide. A drop of 10% KOH was poured on specimen and coverslip was placed over it. The slide was heated gently over the flame and examined under microscope (400 X magnification) after few minutes.

   -FUNGAL CULTURE- SABOURAUD DEXTROSE AGAR Medium was used.

   Two sets of sebouraud dextrose agar (SDA) tubes , one tube containing SDA with antibiotics and cycloheximide , other tube containing SDA with antibiotics and without cycloheximide .SDA plants were incubated at 25^0 C and 37^0 C and were examined for growth daily for first week and twice a week for subsequent period of 3 weeks .

5. Treatment Modality given:

- Surgical Debridement – Radical/Local, with/without orbital exenteration
- Amphotericin B alone
- Amphotericin B with surgical debridement

6. Histopathological assessment of debrided tissue
7. Patients were assessed postoperately to know the outcome of disease and any untoward sequelae.

Number of Cases/ duration of study - Patients admitted with clinical and tissue diagnosis of sinonasalmucormycosis over a period of 1 year (January 2018 to December 2018) were analysed.

Outcome- Outcome of the study was based on the clinical profile of the patients, various associated co-morbidities and surgical and medical therapeutics.

STATISTICAL ANALYSIS

Statistical analysis of the results of study was described in terms of range, mean±standard deviation (±SD), frequencies (No of cases) and relative frequencies (%age) as appropriate. Chi square test was performed for analyzing categorical data.A probability value (pvalue) less than 0.05 was considered statistically significant . All statistical calculations were done using SPSS (statistical package for the social science) SPSS 21.0 version statistical program for Microsoft windows.

OBSERVATIONS AND RESULTS

PATIENT CHARACTERISTICS-

In the present prospective study, 40 patients admitted with clinical and tissue diagnosis of sinonasal mucormycosis over a period of 1 year (January 2018 to December 2018) were analysed. Surgical and medical intervention was carried out in the department of Otorhinolaryngology and Head & Neck surgery Dayanand Medical College& Hospital Ludhiana.

Observation and results were analysed from the under mentioned aspects –

A) Demographic profile

B) Clinical profile

C) Comorbid conditions

D) Endoscopic profile

E) Orbital profile

F) Neurological profile

G) Imaging Study profile

H) Mycological profile

I) Medical Therapeutics

J) Surgical Therapeutics

K) Post Treatment Follow Up

L) Outcome

A) DEMOGRAPHIC PROFILE

TABLE - I

AGE DISTRIBUTION OF PATIENTS

(n=40)

Age group(years)	No. of patients	% of patients
21-30	6	15.0%
31-40	8	20.0%
41-50	11	27.5%
51-60	8	20.0%
>60	7	17.5%
Total number of patients	40	100.0%

n=total number of patients %=percentage of patients

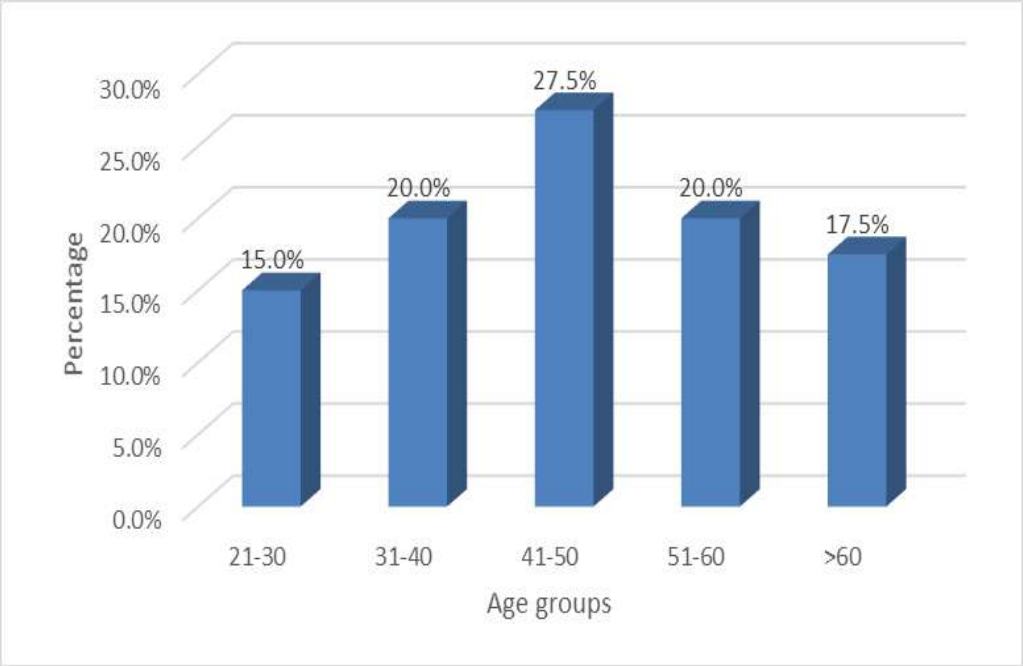
Maximum number of patients were in the age group of 41-50 yrs (27.5 %)

The minimum age was 23 yrs and maximum age 76 yrs.

FIGURE - I

AGE DISTRIBUTION OF PATIENTS

(n=40)



41-50 years (27.5%) was the predominant age group in our study.

TABLE -II

GENDER DISTRIBUTION OF PATIENTS

(n=40)

Gender	No. of patients	% of patients
Female	10	25.0%
Male	30	75 %
Total number of patients	40	100.0%

n=Total number of patients %=percentage of patients

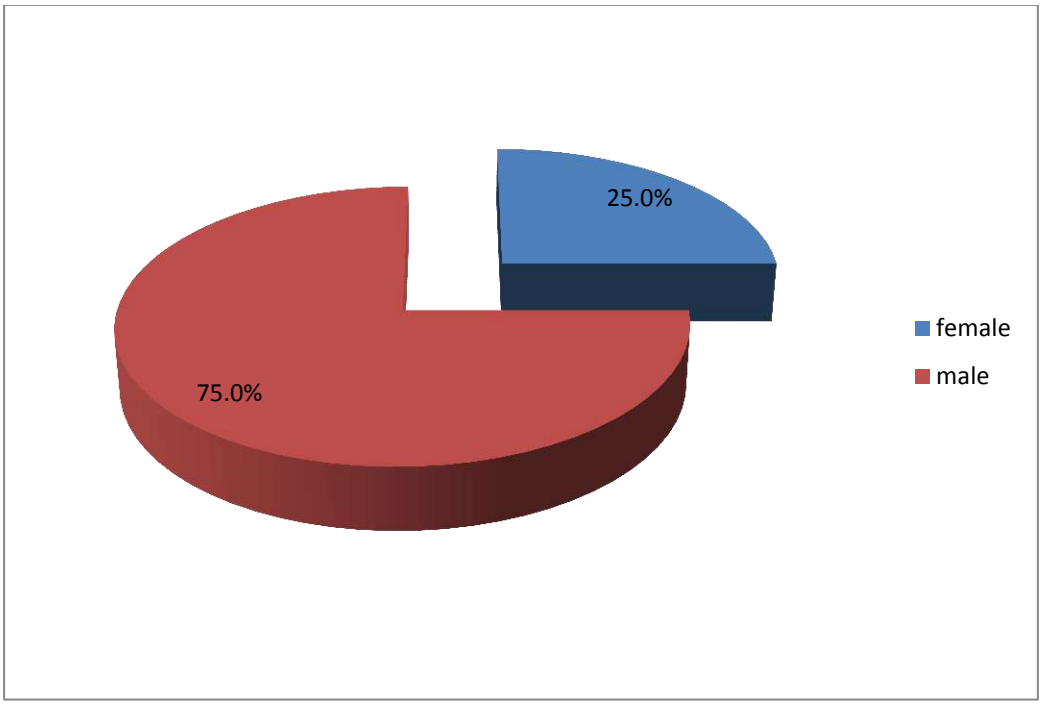
Male patients 30 (75%) outnumbered the female patients (25%) in our study.

The selection of patients was random and irrespective of gender.

FIGURE-II

GENDER DISTRIBUTION OF PATIENTS

(n=40)



Male patients (75%) out numbered the female patients.

TABLE –III

GEOGRAPHIC DISTRIBUTION OF PATIENTS

(n=40)

State	No of patients	% of patients
Punjab	37	92.5%
Outside Punjab	3	7.5%
total number of patients	40	100

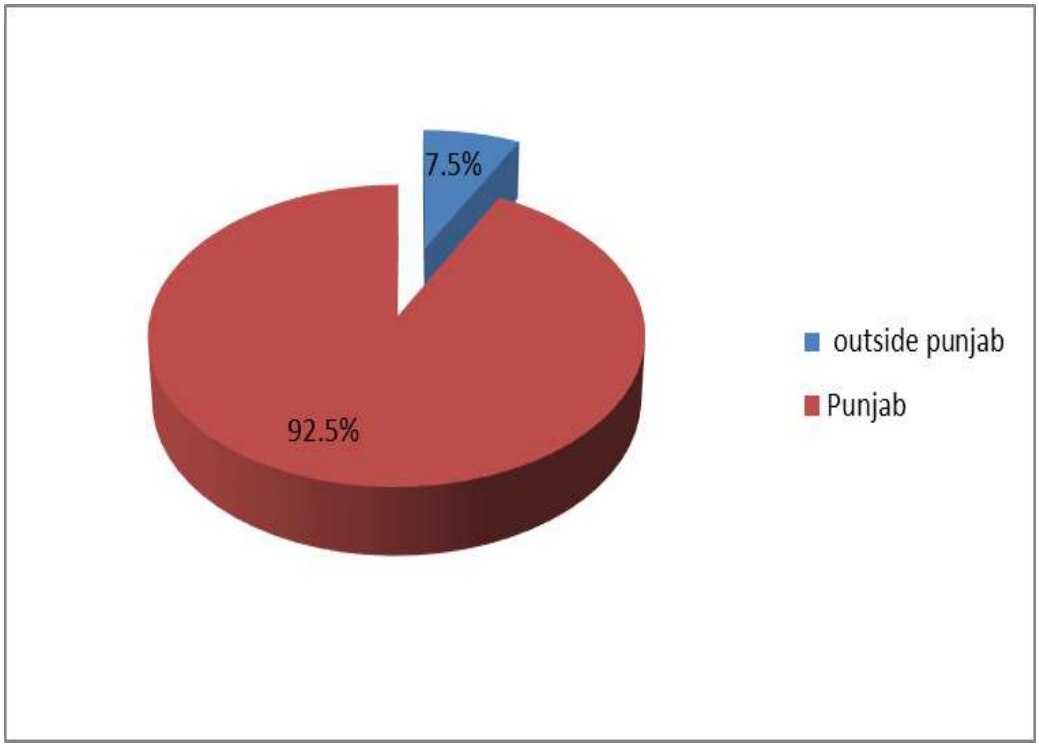
n=Total number of patients %=percentage of patients

Majority of patients (92.5%) were residents of the state of Punjab in our study

FIGURE -III

GEOGRAPHIC DISTRIBUTION OF PATIENTS

(n=40)



Majority of patients (92.5%) were residents of the state of Punjab in our study

TABLE-III A

GEOGRAPHIC SUBDISTRIBUTION OF PATIENTS

(n=40)

Zones of the state of Punjab	No of patients	% of patients
Central	13	35.1%
Northern	7	18.9%
Eastern	2	5.4%
Western	8	21.6%
South west	4	10.8%
Southern	3	8.1%
Total number of patients	37	100.0%

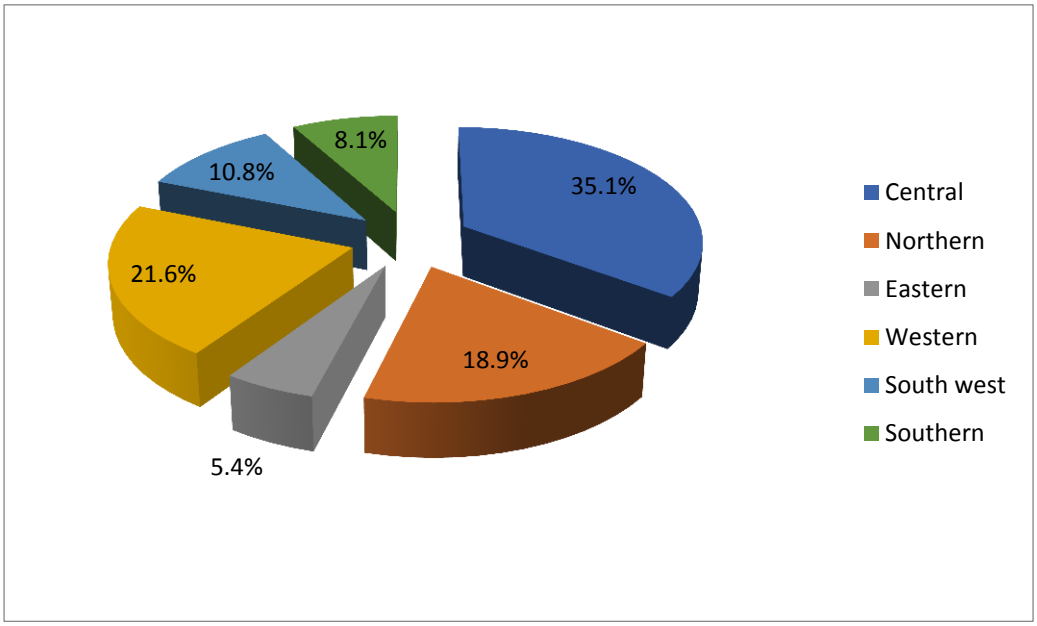
n=Total number of patients %=percentage of patients

Majority of patients were residents of the central zone (35.1%) of Punjab followed by western zone (21.6%) of Punjab. The North zone comprised Amritsar, Pathankot, Jalandhar, Hoshiarpur, West zone- Muktsar, Ferozpur, Fazilka, South West zone - Barnal, Bathinda, South zone- Malerkotla, Sangrur, East Zone- Fatehgarh, SAS Nagar, Central Zone- Ludhiana, Moga.

FIGURE-III A

GEOGRAPHIC SUBDISTRIBUTION OF PATIENTS

(n=40)



Majority of patients were residents of central zone (35.1%) of Punjab.

TABLE-IV

OCCUPATION OF PATIENTS

(n=40)

Occupation	No. of patients	% of patients
Buisnessmen	3	7.5%
Dependent on others	6	15.0%
Farmers	13	32.5%
Housewives	10	25.0%
Labourers	1	2.5%
Students	4	10.0%
Teachers	3	7.5%
Total number of patients	40	100.0%

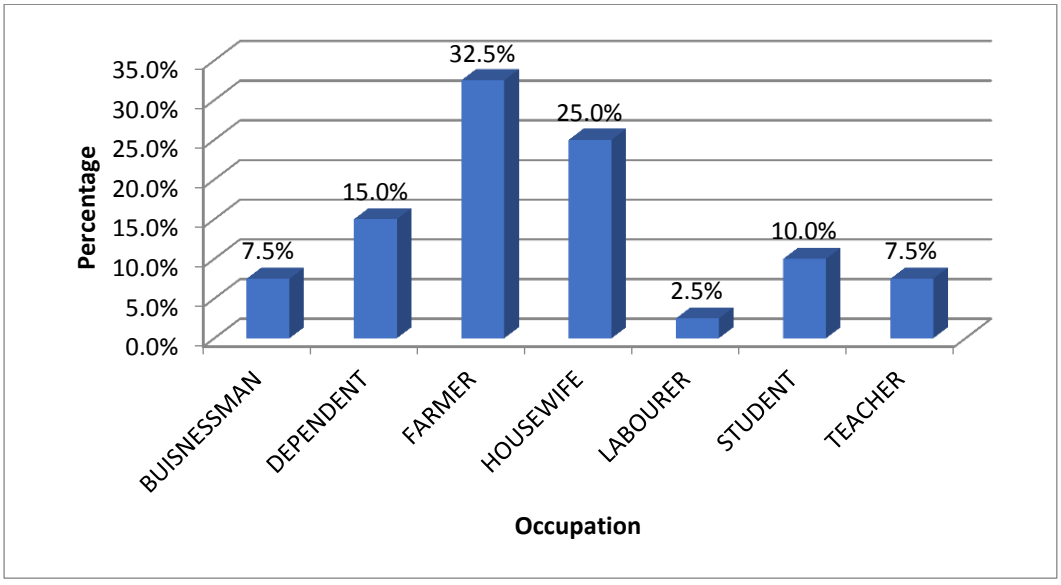
n=Total number of patients %=percentage of patients

Majority of patients in our study were from rural background and farmers (32.5%) by occupation

FIGURE-IV

OCCUPATION OF PATIENTS

(n=40)



Majority of patients in our study were farmer by occupation (32.5%).

B) CLINICAL PROFILE

TABLE-V

PATIENT PRESENTATION

(n=40)

Patient symptoms/signs	No. of patients	% of patients
Nasal	26	65.0%
Facial	22	55.0%
Ocular	29	72.5%
Combined	12	30.0%

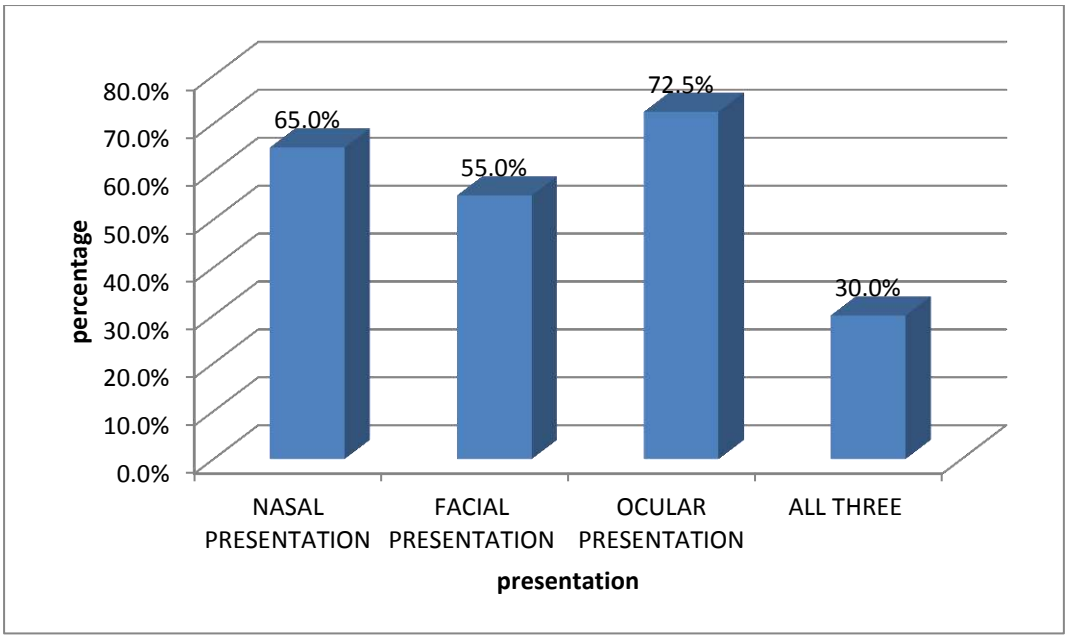
n=total number of patients %=percentage of patients

72.5% of the patients had ocular presentation followed by nasal presentation (65%). Only 12 patients (30%) presented with advanced disease with nasal, ocular and facial involvement in our study.

FIGURE-V

PATIENT PRESENTATION

(n=40)



72.5% of the patients had ocular presentation followed by nasal presentation (65%). 30% presented with advanced disease with nasal, ocular and facial involvement in our study.

TABLE-VI

DISTRIBUTION OF VARIOUS SYMPTOMS

(n=40)

Symptoms	No of patients	% of patients
Nasal crusting	21	52.5%
Rhinorrhea	25	62.5%
Nasal Obstruction	24	60.0%
Facial Hypoesthesia	19	47.5%
Facial Swelling	18	45.0%
Facial Paralysis	5	12.5%
Lacrimation	14	35.0%
Periorbital swelling	28	70.0%
Proptosis	25	62.5%
Vision loss	27	67.5%
Diplopia	20	50.0%

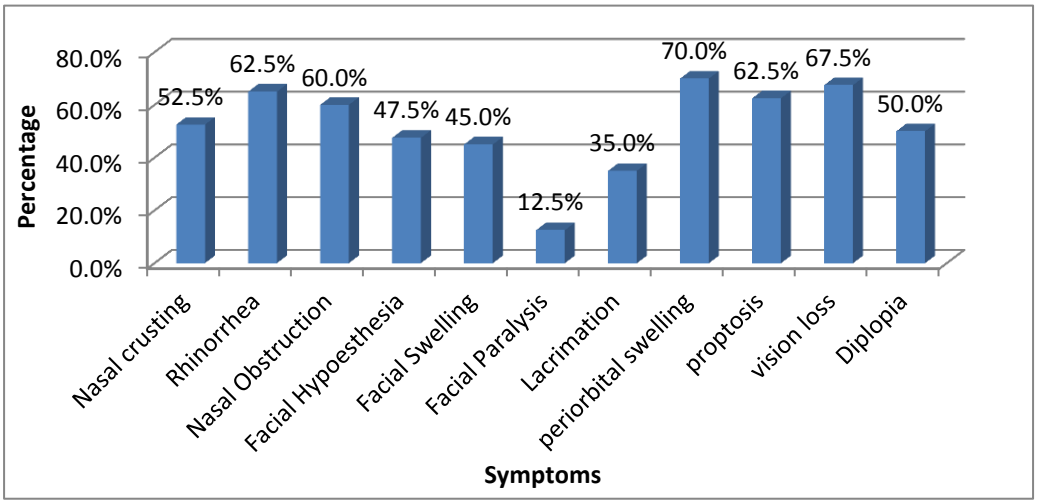
n=total number of patients %=percentage of patients

Maximum patients presented with periorbital swelling (70%) in our study followed by vision loss (67.5%) and rhinnorhea (62.5%).

FIGURE-VI

DISTRIBUTION OF VARIOUS SYMPTOMS

(n=40)



Maximum patients presented with periorbital swelling (70%) in our study followed by vision loss (67.5%) and rhinnorhea (62.5%).

TABLE-VII

ASSOCIATED SYMPTOMS

(n=40)

Associated Symptoms	No of patients	% of patients
Headache	32	80.0%
Fever	29	72.5%

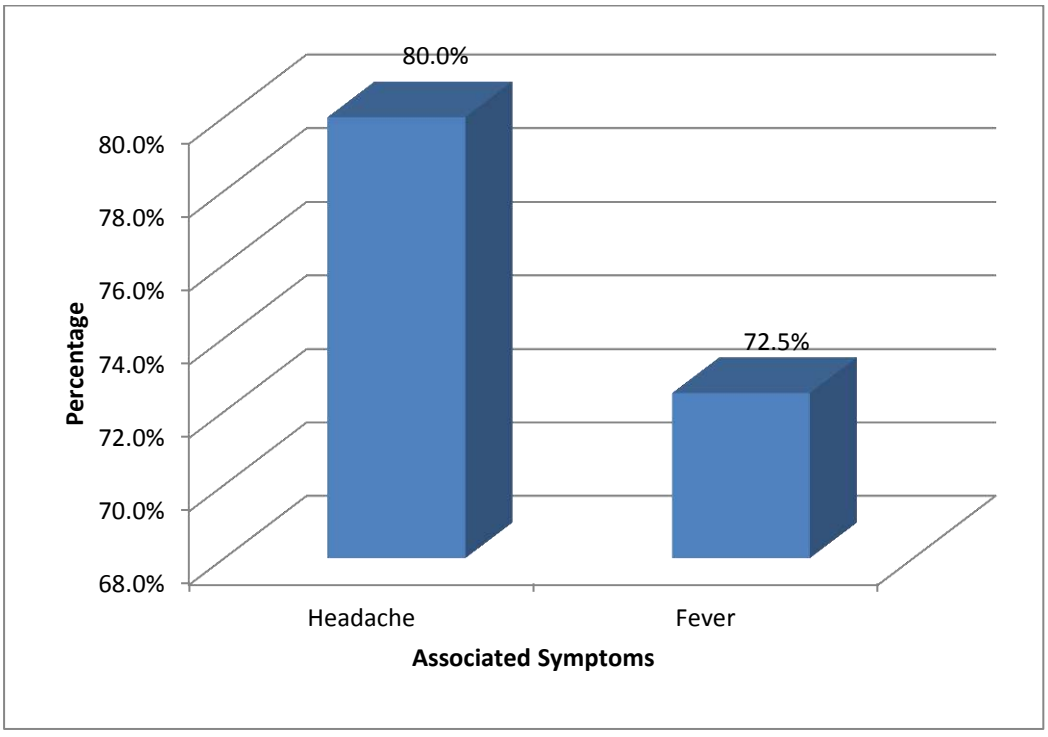
n=total number of patients %=percentage of patients

80% of patients had history of headache and 72.5% of the patients had fever present in our study.

FIGURE -VII

ASSOCIATED SYMPTOMS

(n=40)



80% of patients had history of headache and 72.5% of the patients had fever present in our study.

i) NASAL PRESENTATION

TABLE-VIII

NASAL SYMPTOMS

(n=40)

Nasal symptoms	No of patients	% of patients
Crusting nose	21	52.5%
Rhinorrhea	25	62.5%
Obstruction nose	24	60.0%

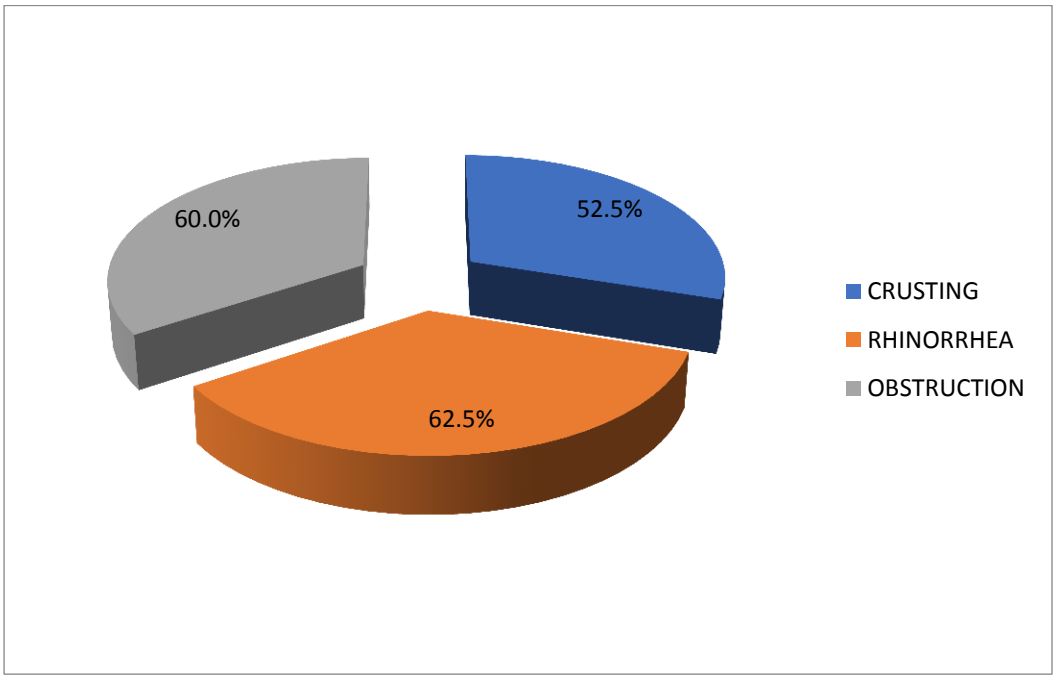
n=Total number of patients %= percentage of patients

Rhinorrhea (62.5%), nasal obstruction (60%) and crusting (52.5%) were notable nasal symptoms in our study

FIGURE-VIII

NASAL SYMPTOMS

(n=40)



Rhinorrhea (62.5%) was the most common nasal symptom.

TABLE-IX

LATERALITY OF NASAL CRUSTING

(n=21)

Laterality of crusting	No. of patients	% of patients
Right	7	33.3%
Left	14	66.7%
Total number of patients	21	100.0%

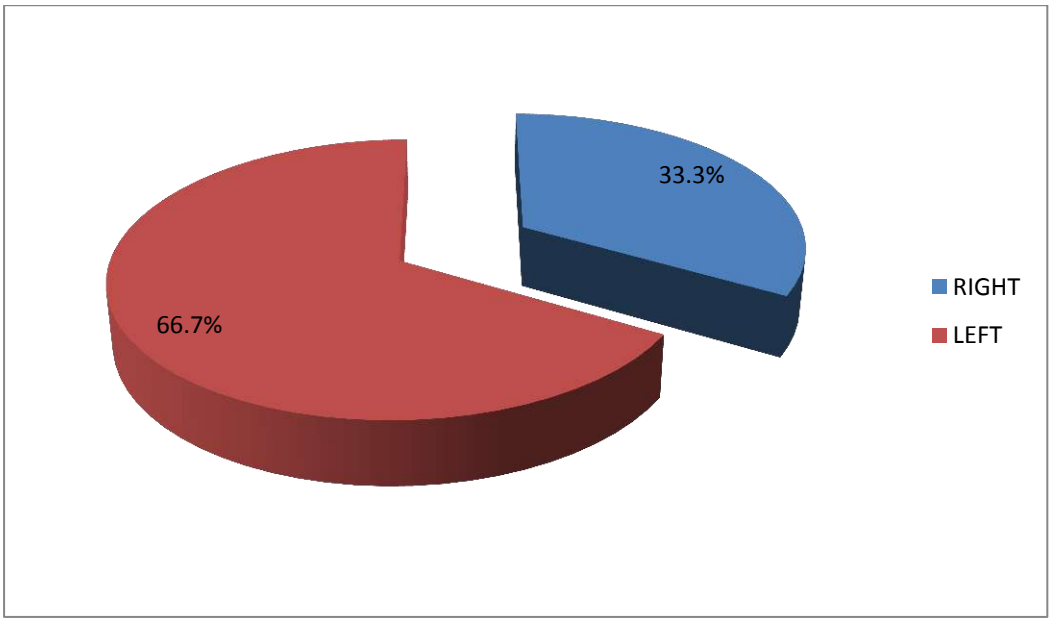
n=Total number of patients %=percentage of patients

In our study 21 patients had nasal crusting with left side (66.7%) being predominant side of the involved nasal cavity

FIGURE-IX

LATERALITY OF NASAL CRUSTING

(n=21)



Left side is predominantly involved in our study.

TABLE-X

LATERALITY OF NASAL OBSTRUCTION

(n=24)

Laterality of obstruction	No. of patients	% of patients
RIGHT	8	33.3%
LEFT	16	66.7%
Total number of patients	24	100.0%

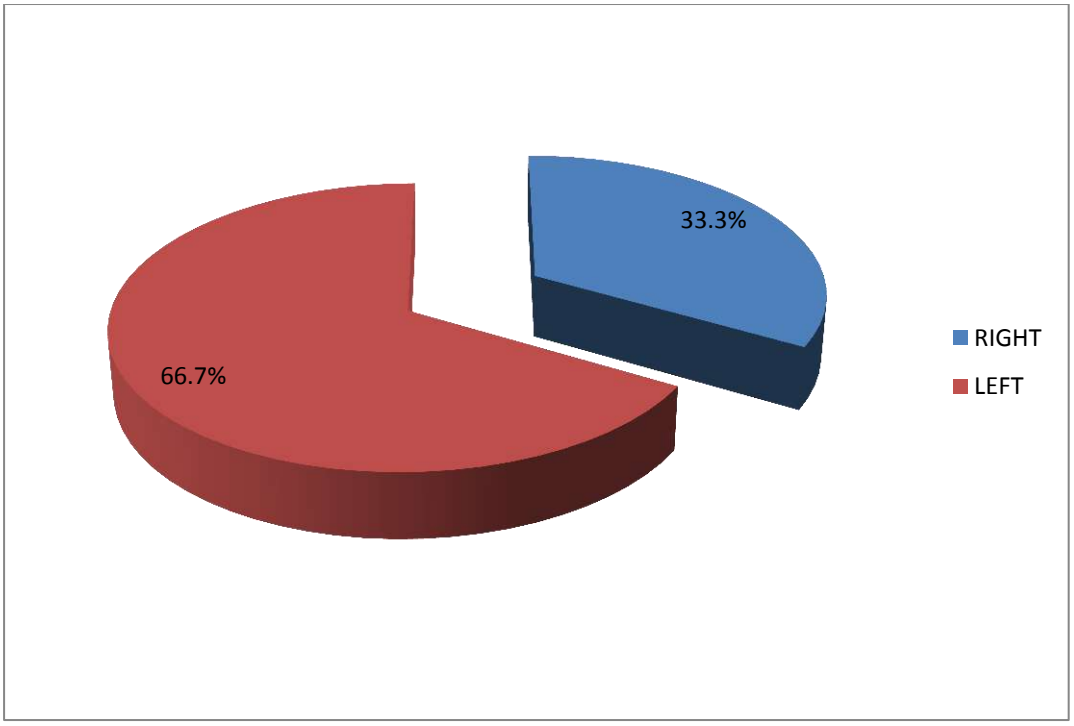
n=Total number of patients %=percentage of patients

Maximum patients had left sided nasal obstruction (66.7%) in our study.

FIGURE-X

LATERALITY OF NASAL OBSTRUCTION

(n=24)



Left sided nasal obstruction was predominant in our study.

TABLE-XI

DURATION OF NASAL SYMPTOMS

(n=26)

Duration of nasal symptoms	No. of patients	% of patients
<1week	2	7.7%
1-2 weeks	5	19.2%
>2 weeks	19	73.1%

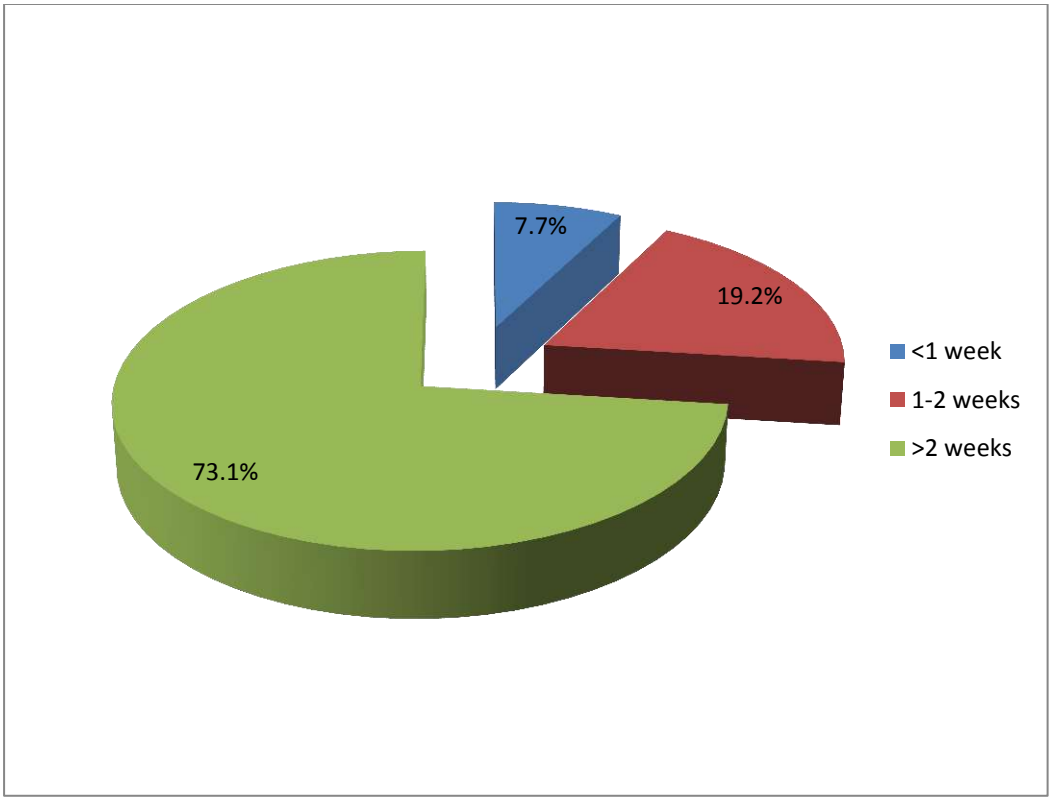
n=Total number of patients %=percentage of patients

Maximum number of patients (19) had nasal symptoms of duration (73.1%) more than 2 weeks in our study.

FIGURE-XI

DURATION OF NASAL SYMPTOMS

(n=26)



Most patients presented late, i.e. with duration of nasal symptoms of duration more than 2 weeks (73.1%).

ii) FACIAL PRESENTATION

TABLE-XII

FACIAL SYMPTOMS

(n=40)

Facial symptoms	No. of patients	% of patients
Hypoesthesia	19	47.5%
Swelling	18	45.0%
Paralysis	5	12.5%

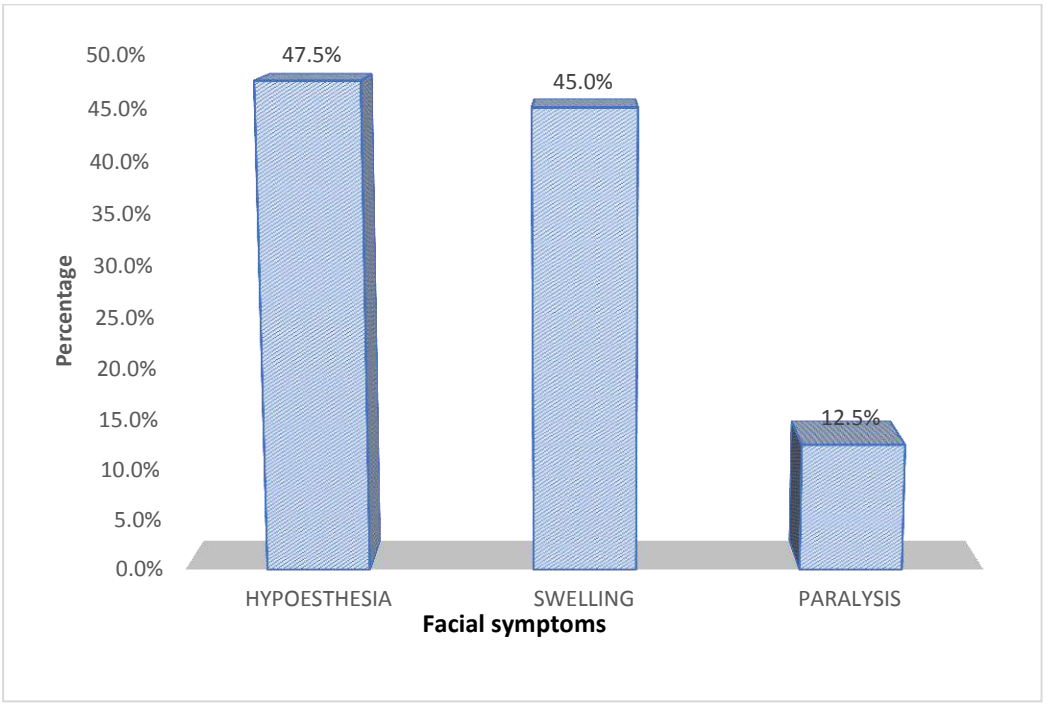
n=Total number of patients %=percentage of patients

In the facial presentation group maximum number of patients presented with facial hypoesthesia (47.5%) followed by facial swelling (45%) in our study.

FIGURE-XII

FACIAL SYMPTOMS

(n=40)



Facial hypoesthesia (47.5%) followed by facial swelling (45%) and paralysis (12.5%) was noted in our study.

TABLE-XIII

LATERALITY OF FACIAL SYMPTOMS

(n=19)

Laterality of facial symptoms	No. of patients	% of patients
Right	7	36.8%
Left	12	63.2%
Total number of patients	19	100.0%

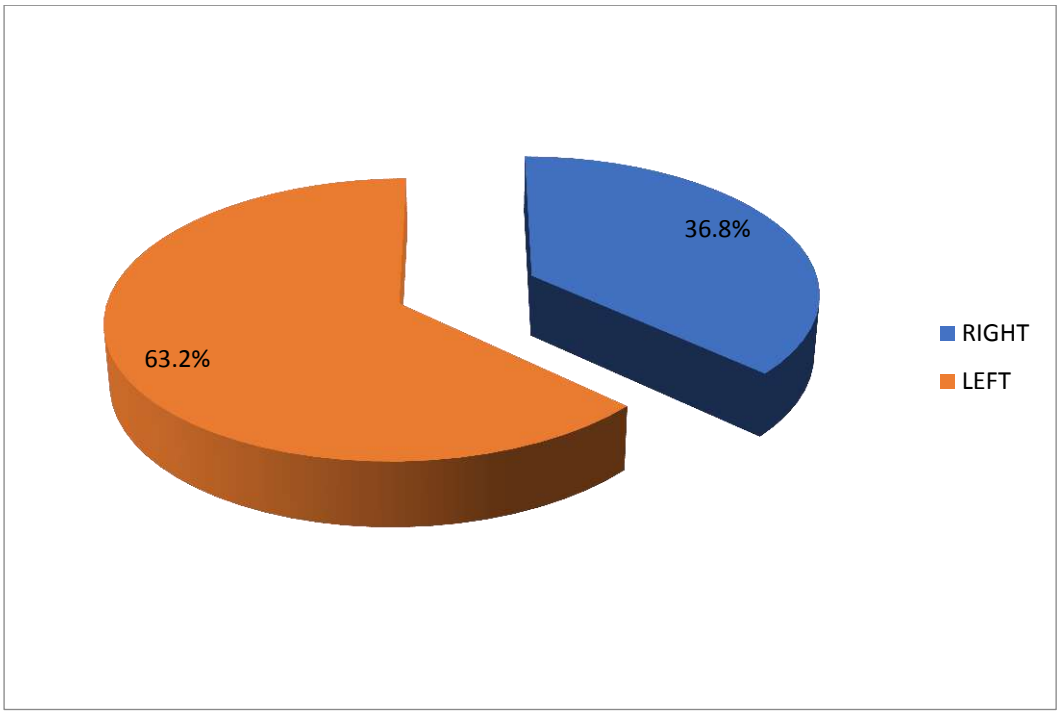
n=Total number of patients %=percentage of patients

Left sided facial symptomatology was predominant in our study (63.2%).

FIGURE-XIII

LATERALITY OF FACIAL SYMPTOMS

(n=19)



Left side involvement was predominant in our study with 63.2%.

TABLE-XIV

DURATION OF FACIAL SYMPTOMS

(n=22)

Duration of facial symptoms	No. of patients	% of patients
<1 week	6	27.3%
1-2 weeks	4	18.2%
>2 weeks	12	54.5%

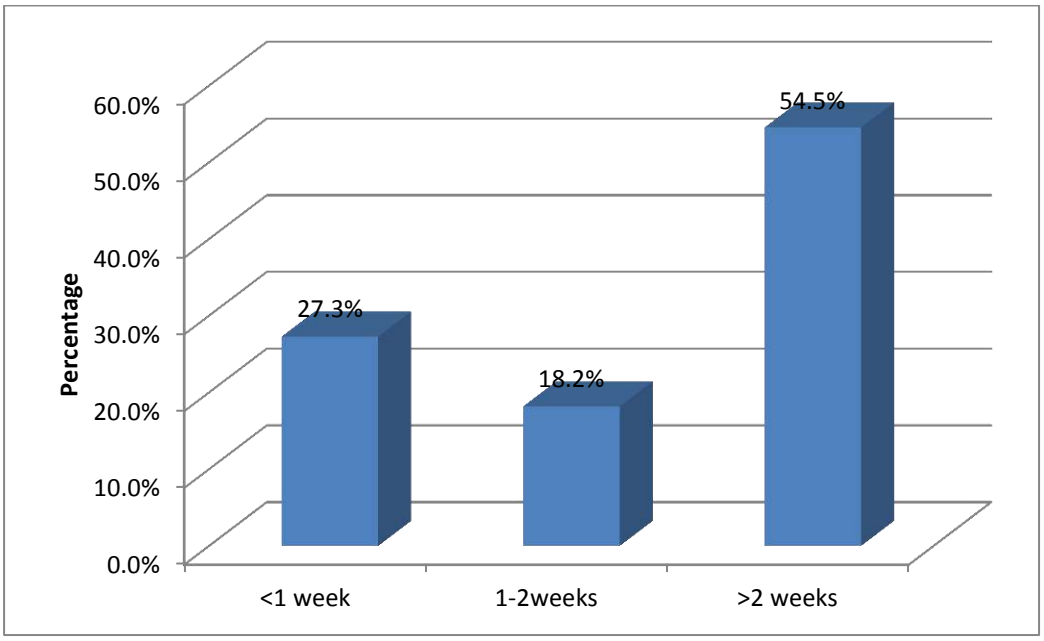
n=Total number of patients %=percentage of patients

Maximum number of patients (54.5%) presented with facial symptoms of duration more than 2 weeks in our study.

FIGURE-XIV

DURATION OF FACIAL SYMPTOMS

(n=22)



Maximum number of patients (54.3%) presented with facial symptoms of duration more than 2 weeks in our study.

iii) OCULAR PRESENTATION

TABLE-XV

OCULAR SYMPTOMS

(n=40)

Ocular symptoms	No. of patients	% of patients
Lacrimation	14	35.0%
Periorbital swelling	28	70.0%
Vision loss	27	67.5%
Diplopia	20	50%

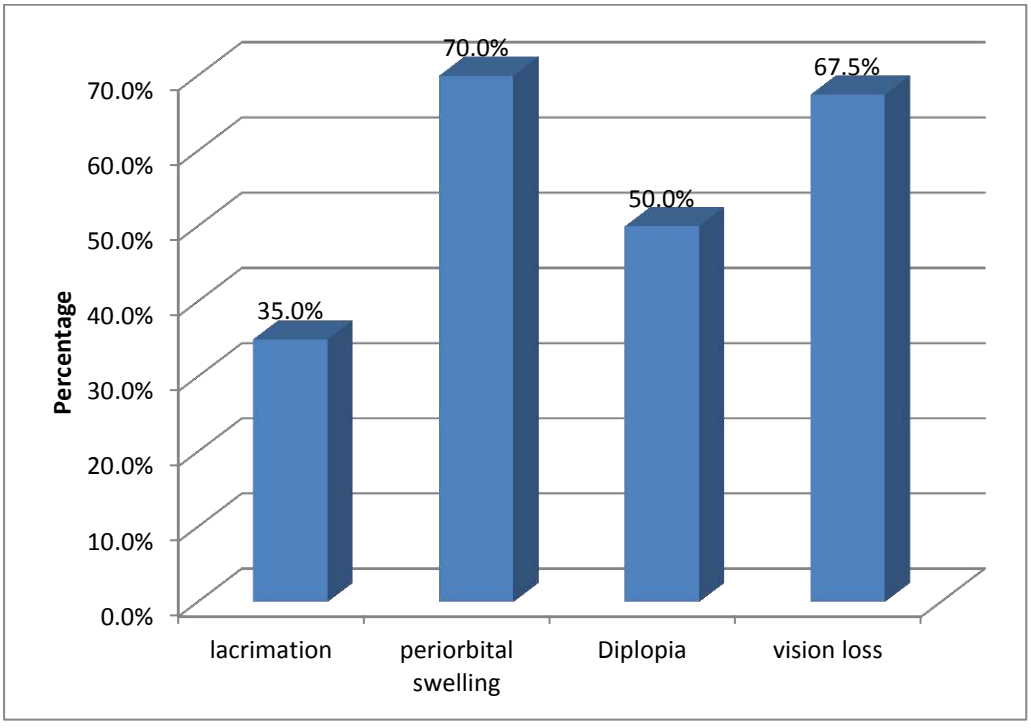
n=total number of patients %=percentage of patients

Periorbital swelling (70%) was the most common ocular symptom followed by vision loss (67.5%) in our study.

FIGURE-XV

OCULAR SYMPTOMS

(n=40)



Periorbital swelling (70%) was the most common ocular symptom followed by vision loss (67.5%) in our study.

TABLE-XVI

DURATION OF OCULAR SYMPTOMS

(n=29)

Duration of ocular symptoms	No. of patients	% of patients
< 1week	25	86.2%
> 1 week	4	13.8%

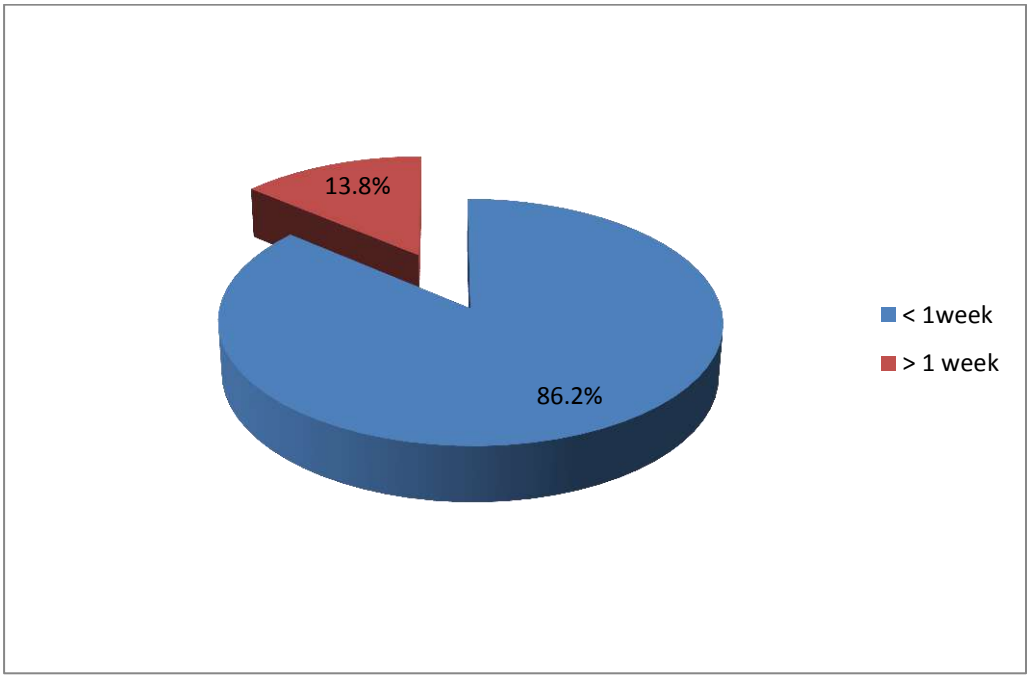
n=total number of patients %=percentage of patients

Ocular symptoms had duration of less than a week in 86.2% of the patients.

FIGURE-XVI

DURATION OF OCULAR SYMPTOMS

(n=29)



Ocular symptoms had duration of less than a week in 86.2% of the patients

TABLE-XVII

LATERALITY OF PERIORBITAL SWELLING

(n=28)

Laterality of periorbital swelling	No. of patients	% of patients
Right	9	32.1%
Left	19	67.9%
Total	28	100.0%

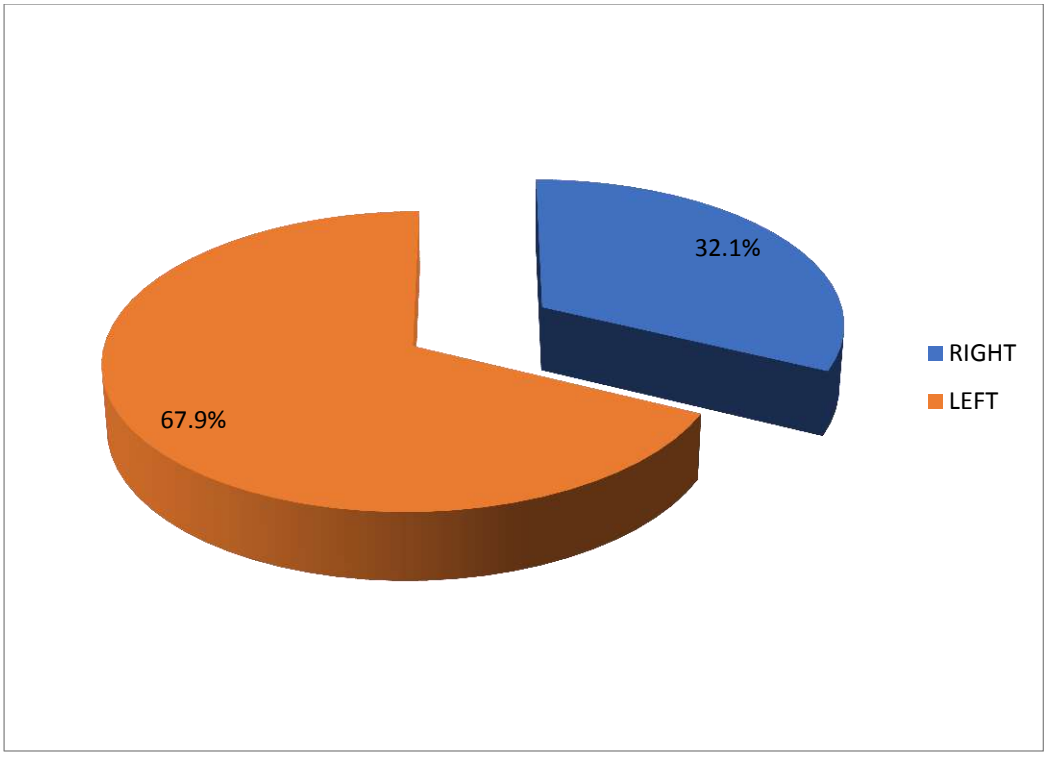
n=total number of patients %=percentage of patients

67.9% of patients had periorbital swelling of left side in our study.

FIGURE-XVII

LATERALITY OF PERIORBITAL SWELLING

(n=28)



67.9 % of patients had periorbital swelling of left side.

TABLE-XVIII

LATERALITY OF LACRIMATION

(n=14)

Laterality of lacrimation	No. of patients	% of patients
RIGHT	6	42.9%
LEFT	8	57.1%
Total	14	100.0%

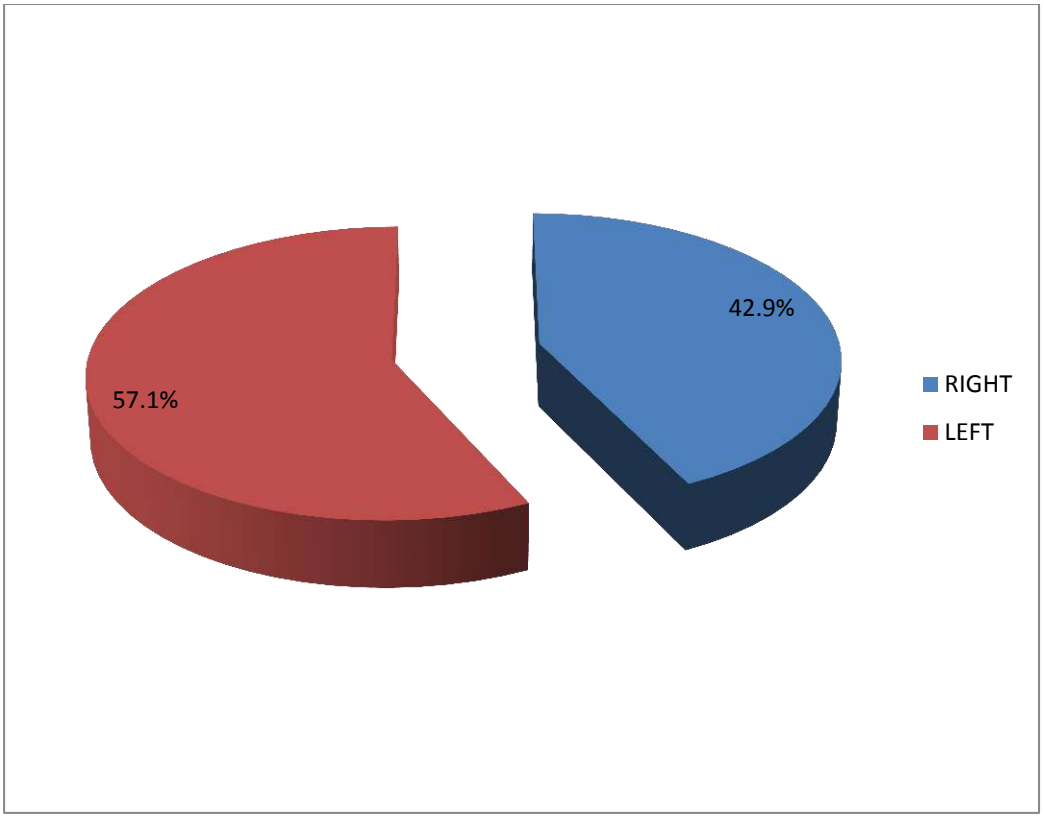
n=total number of patients %=percentage of patients

Left eye was predominantly involved in 57.1% of the patients in our study.

FIGURE-XVIII

LATERALITY OF LACRIMATION

(n=14)



Left eye was predominantly involved in 57.1% of the patients in our study

TABLE-XIX

LATERALITY OF VISION LOSS

(n=27)

Laterality of vision loss	No. of patients	% of patients
Right	9	33.3%
Left	18	66.7%
Total number of patients	27	100.0%

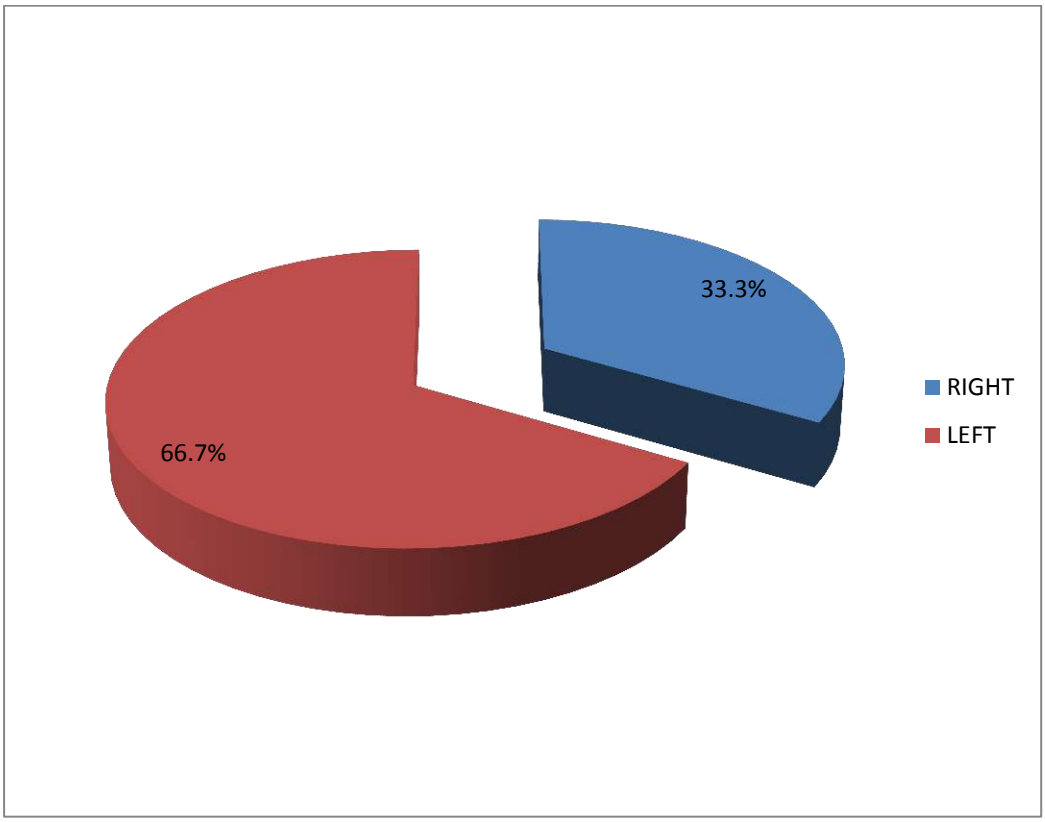
n=total number of patients %=percentage of patients

In our study 66.7 % patients had vision loss in left eye.

FIGURE-XIX

LATERALITY OF VISION LOSS

(n=27)



In our study 66.7% patients had vision loss in left eye

iv) MULTIPLE SITE INVOLVEMENT

TABLE-XX

MULTIPLE SITE INVOLVEMENT OF FACE

(n=40)

Multiple site involvement	No of patients	% of patients
Nasal mucosa	40	100.0%
Palate	9	22.5%
Skin	9	22.5%

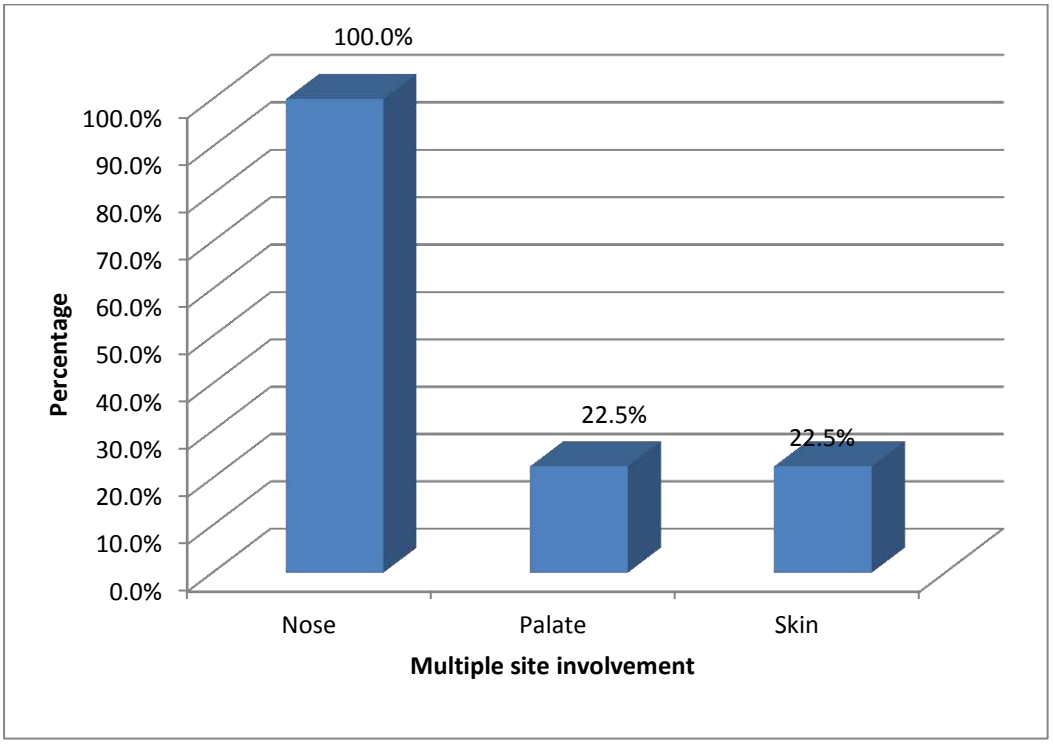
n=total number of patients %=percentage of patients

Nasal mucosa was involved in all the patients while palatal necrosis and skin eschar was present in 22.5 % of the patients in our study.

TABLE-XX

MULTIPLE SITE INVOLVEMENT OF FACE

(n=40)



Nasal mucosa was involved in all the patients while palatal necrosis and skin eschar was present in 22.5 % of the patients in our study.

C)CO-MORBID CONDITIONS

TABLE-XXI

STATUS OF IMMUNITY

(n=40)

Status of immunity	No. of patients	% of patients
Immunocompromised	38	95.0%
immunocompetent	2	5.0%
Total number of patients	40	100%

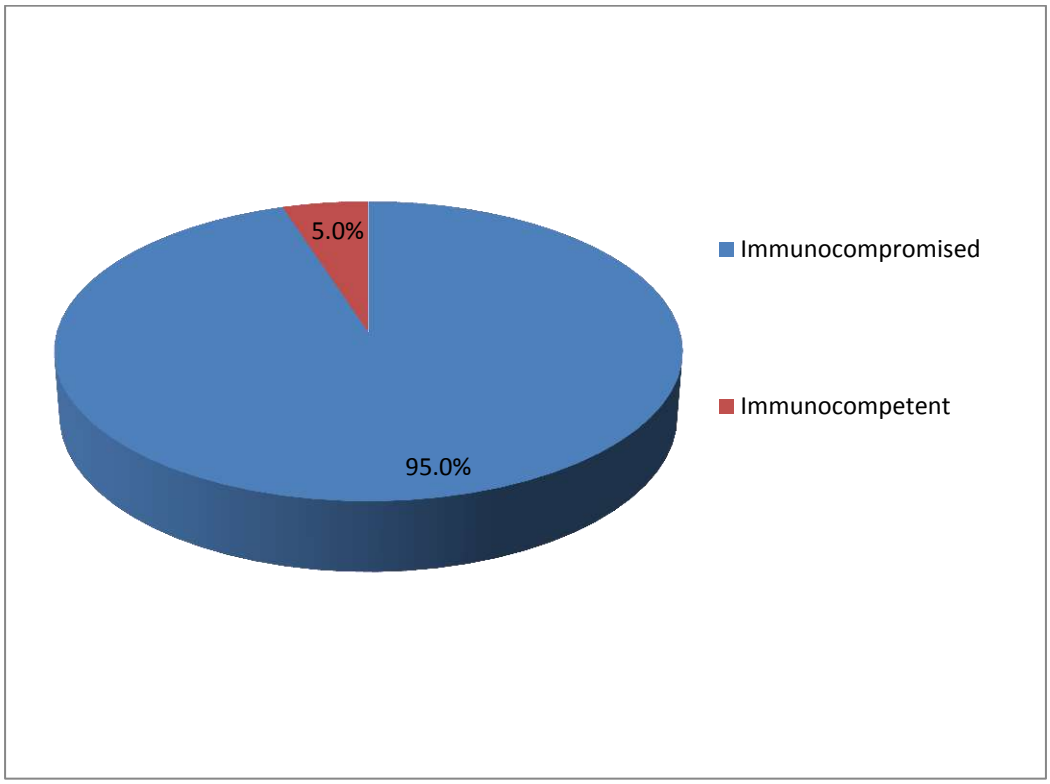
n=total number of patients %=percentage of patients

95% of patients were immunocompromised.

FIGURE-XXI

STATUS OF IMMUNITY

(n=40)



95% of patients were immunocompromised

TABLE-XXII

IMMUNOCOMPROMISED STATE

(n=40)

Immunocompromised state	No. of patients	% of patients
Diabetes mellitus	38	95.0%
Tuberculosis	4	10.0%
Chronic kidney disease	11	27.5%

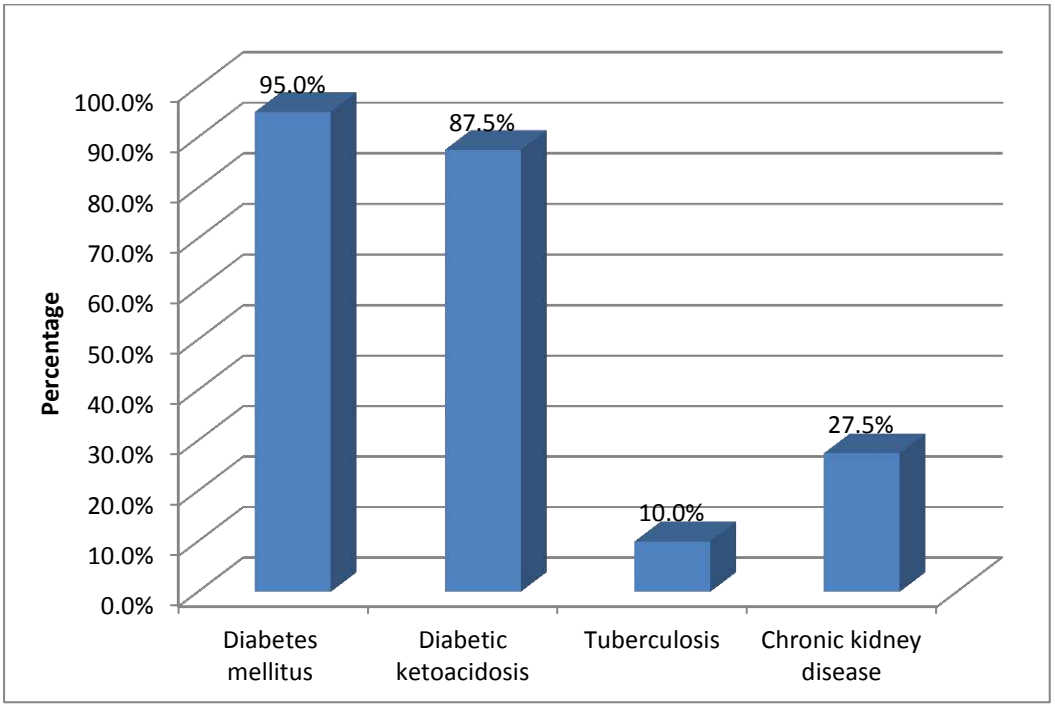
n=total number of patients %=percentage of patients

Diabetes mellitus (95.0%) was the most common underlying immunocompromised state followed by chronic kidney disease (27.5%) in our study.

FIGURE-XXII

IMMUNOCOMPROMISED STATE

(n=40)



Diabetes mellitus was the most common underlying immunocompromised state in our study.

TABLE-XXIII

RISK FACTORS/ADDICTIONS

(n=40)

Risk factors/Addictions	No. of patients	% of patients
Alcohol use	29	72.5%
Smoking	19	47.5%
Drug abuse	23	57.5%
Steroid use	10	25.0%

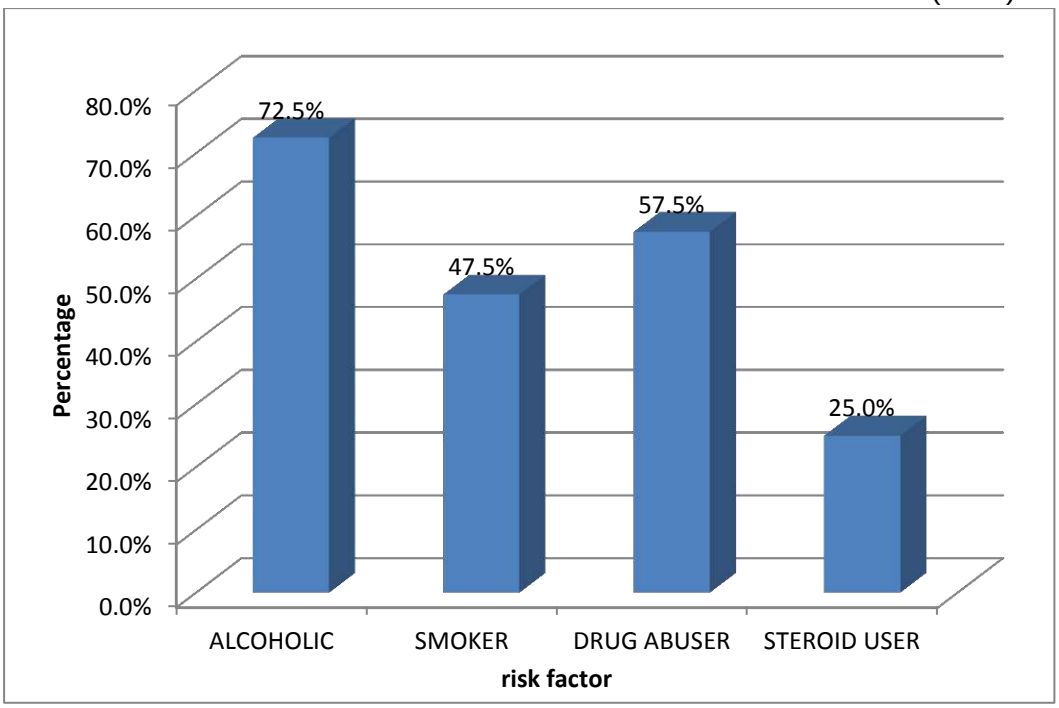
n=total number of patients %=percentage of patients

Alcohol addiction (72.5%) was the most common risk factor followed by drug abuse (57.5%) in our study.

FIGURE-XXIII

RISK FACTORS/ADDICTIONS

(n=40)



Alcohol use (72.5%) was the most common risk factor followed by drug abuse (57.5%) in our study.

TABLE-XXIV

REACTIVE STATUS

(n=4)

Reactive status	No. of patients	% of patients
HBV+	1	25%
HCV+	3	75%
Total number of patients	4	100%

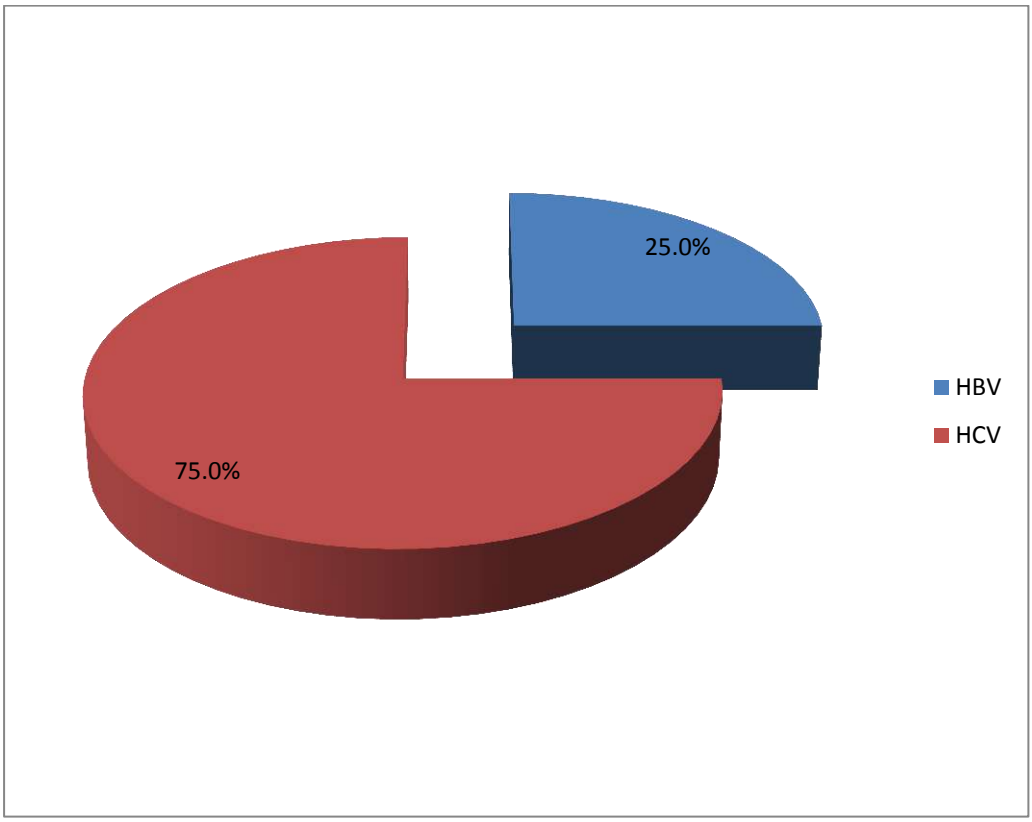
n=total number of patients %=percentage of patients

Total of 4 reactive patients 3 were hepatitis c viral marker reactive in our study.

FIGURE-XXIV

REACTIVE STATUS

(n=4)



Total of 4 reactive patients 3 were hepatitis c viral marker reactive in our study.

TABLE-XXV

PATIENTS IN DIABETIC KETOACIDOSIS

(n=38)

Patients in diabetic ketoacidosis	No. of patients	% of patients
Present	35	92.1%
Absent	3	7.9%
Total number of patients	38	100.0%

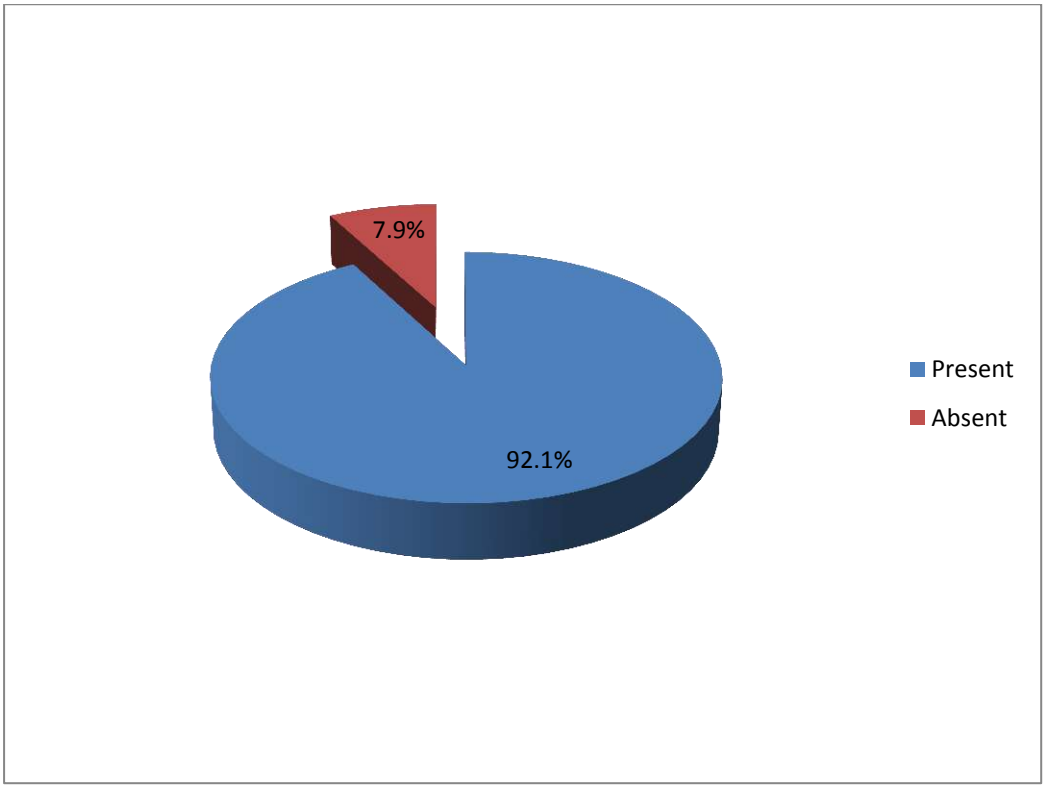
n=total number of patients %=percentage of patients

92.1 % of the diabetic patients were in diabetic ketoacidosis at the time of presentation in our study.

FIGURE-XXV

PATIENTS IN DIABETIC KETOACIDOSIS

(n=38)



92.1% of the diabetic patients were in diabetic ketoacidosis at the time of presentation in our study

TABLE-XXVI

DEARRANGED LAB PARAMETERS

(n=40)

Lab parameters	No. of patients	% of patients
Anaemia (hb<12gm/dl)	37	92.5%
Leucocytosis (tlc>11 x10^9/L)	38	95.0%
Derranged Renal function (serum creatinine >1.5mg/dl)	21	52.5%
Derranged Electrolytes Sodium-<135or>145mEq/L Potassium- <3.5or>5 mEq/L	24	60.0%

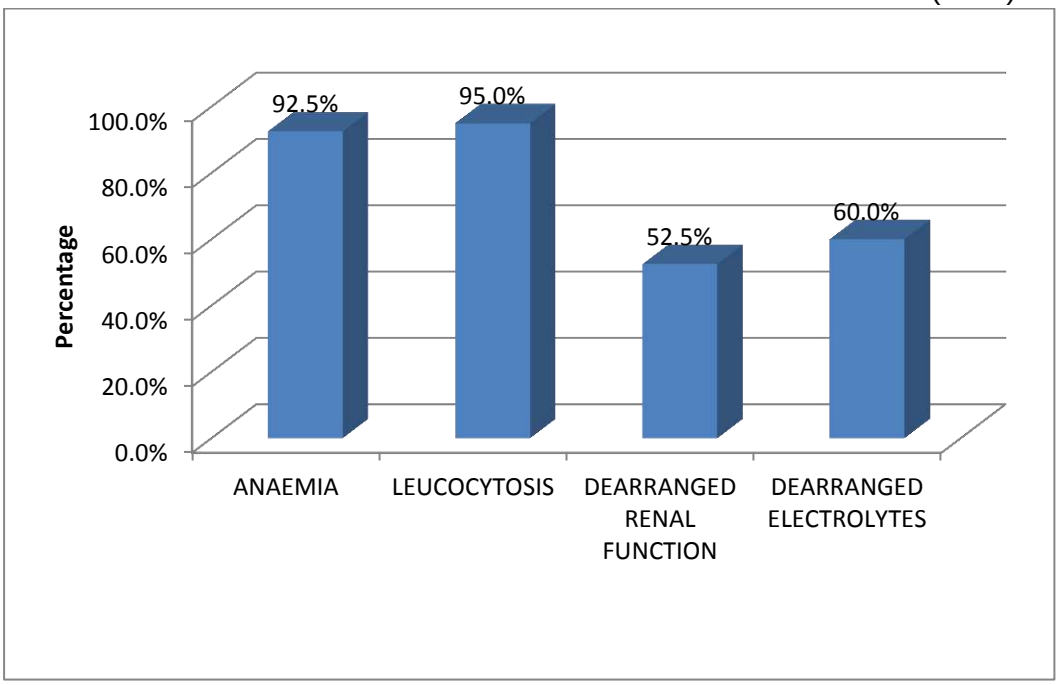
n=total number of patients %=percentage of patients

Anemia was the lab parameter affected most in our study.

FIGURE-XXVI

DEARRANGED LAB PARAMETERS

(n=40)



Anemia was thelab parameter affected most in our study.

D) ENDOSCOPIC PROFILE

TABLE XXVII

INVOLVEMENT OF SITES ON NASAL ENDOSCOPY

(n=40)

Sites	No. of patients	% of patients
Septum	22	55.0%
Inferior turbinate	33	82.5%
Middle turbinate	33	82.5%
Floor	11	27.5%
Mucosal pallor	25	62.5%

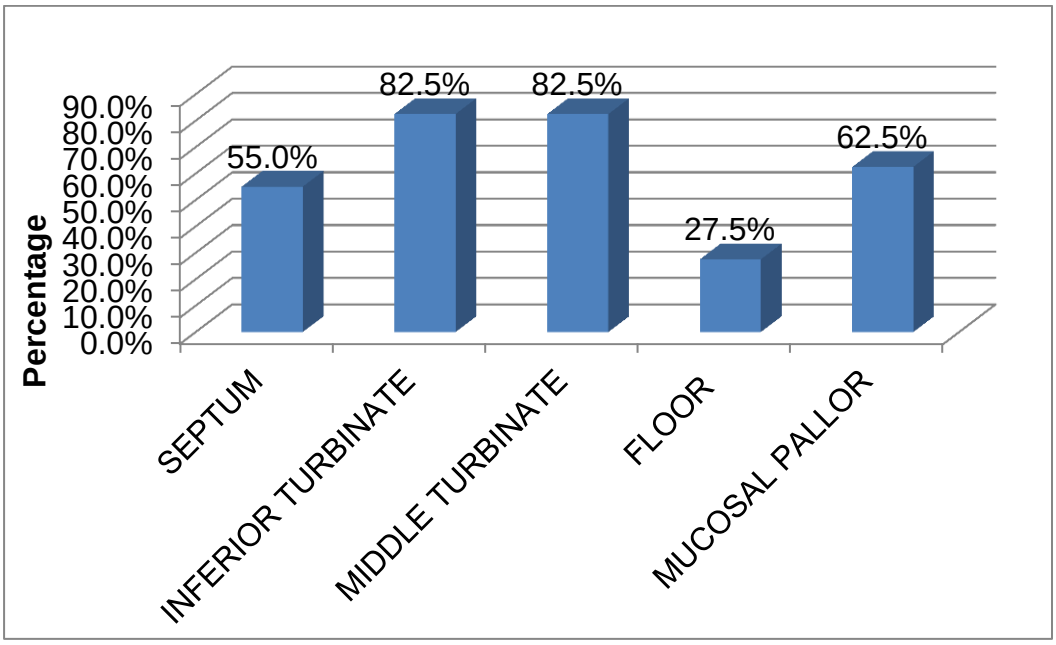
n=total number of patients %=percentage of patients

Middle turbinate (82.5%) and inferior turbinate (82.5%) were the most common sites involved in our study on nasal endoscopy.

FIGURE- XXVII

INVOLVEMENT OF SITES ON NASAL ENDOSCOPY

(n=40)



Middle turbinate (82.5%) and inferior turbinate (82.5%) were the most common sites involved in our study on nasal endoscopy.

TABLE XXVIII

MULTIPLE SITE INVOLVEMENT IN NOSE

(n=40)

Multiple sites	No. of patients	% of patients
Septum +Inferior turbinate+Middle turbinate	19	47.5%
Inferior turbinate +Middle turbinate	28	70.0%
Septum +Inferior turbinate+Middle turbinate + Floor	11	27.5%

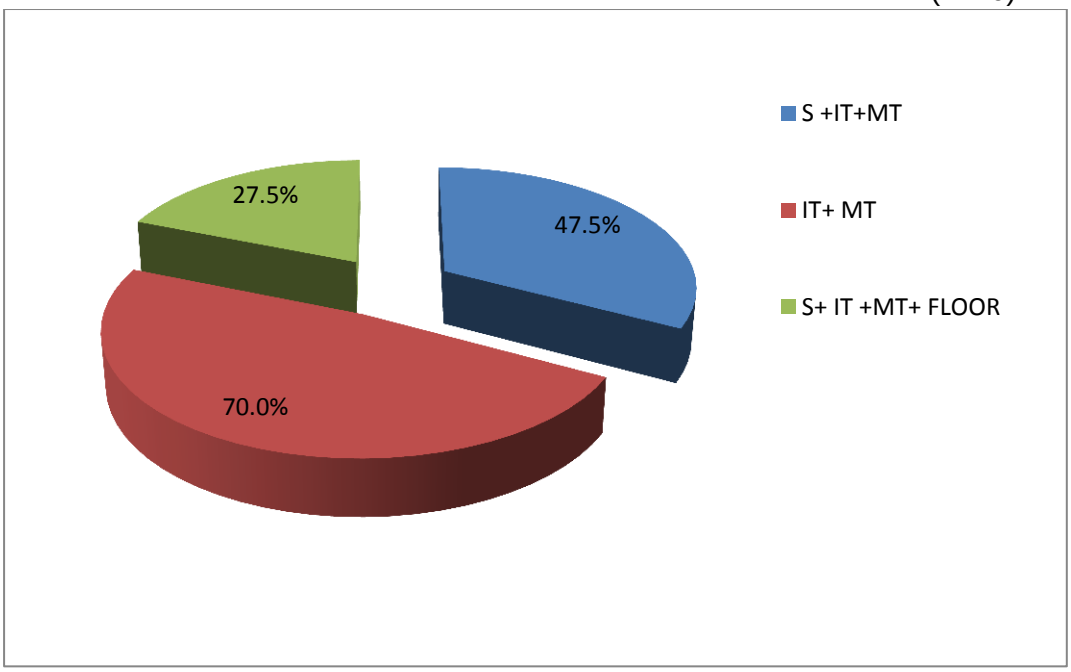
n=total number of patients %=percentage of patients

Inferior and middle turbinate (70%) were most commonly involved in our study.

FIGURE- XXVIII

MULTIPLE SITE INVOLVEMENT

(n=40)



Inferior and middle turbinate (70%) were most commonly involved in our study

E) ORBITAL PROFILE

TABLE-XXIX

INVOLVEMENT OF EXTRAOCULAR MUSCLES

(n=40)

Involvement of extraocular muscles	No. of patients	% of patients
Frozen	18	45.0%
Restricted	8	20.0%
Normal	14	35.0%

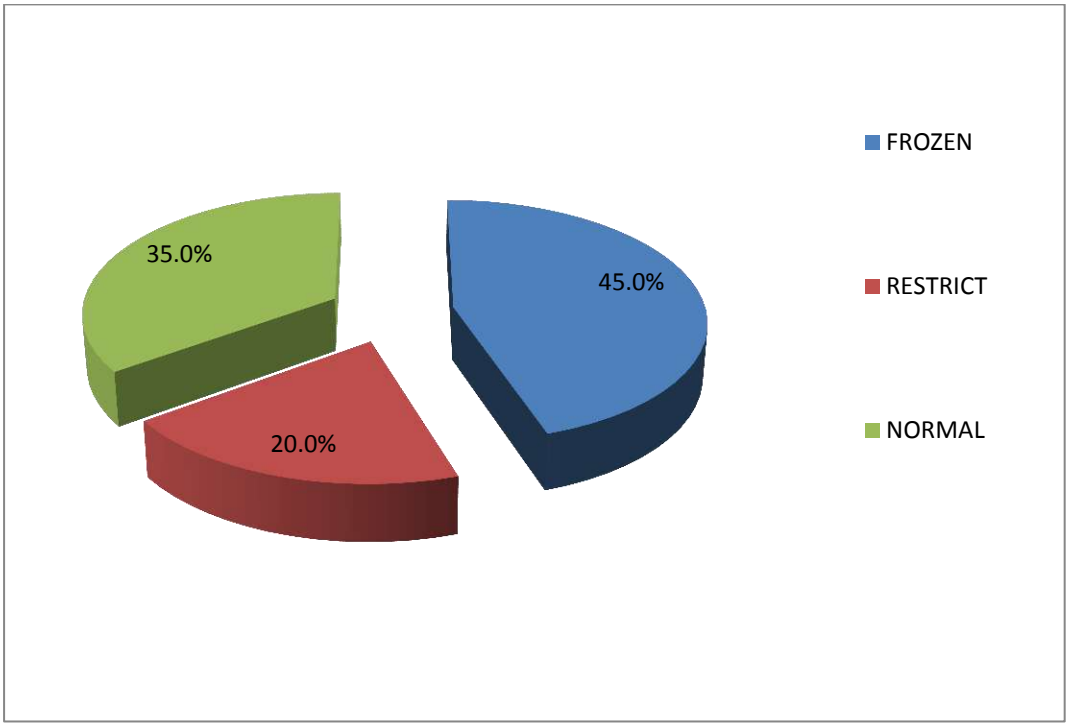
n=total number of patients %=percentage of patients

45% of the patients had frozen eye and 20 % had restricted eye movements while 35 % of the patients had normal extraocular movements

FIGURE-XXIX

INVOLVEMENT OF EXTRAOCULAR MUSCLES

(n=40)



45% of the patients had frozen eye and 20 % had restricted eye movements while 35 % of the patients had normal extraocular movements

TABLE-XXX

OCULAR SIGNS

(n=40)

Ocular signs	No of patients	Percentage
Central retinal artery occlusion	20	50.0%
Total ophthalmoplegia	23	57.5%
Absent pupilary reflex	25	37.5%

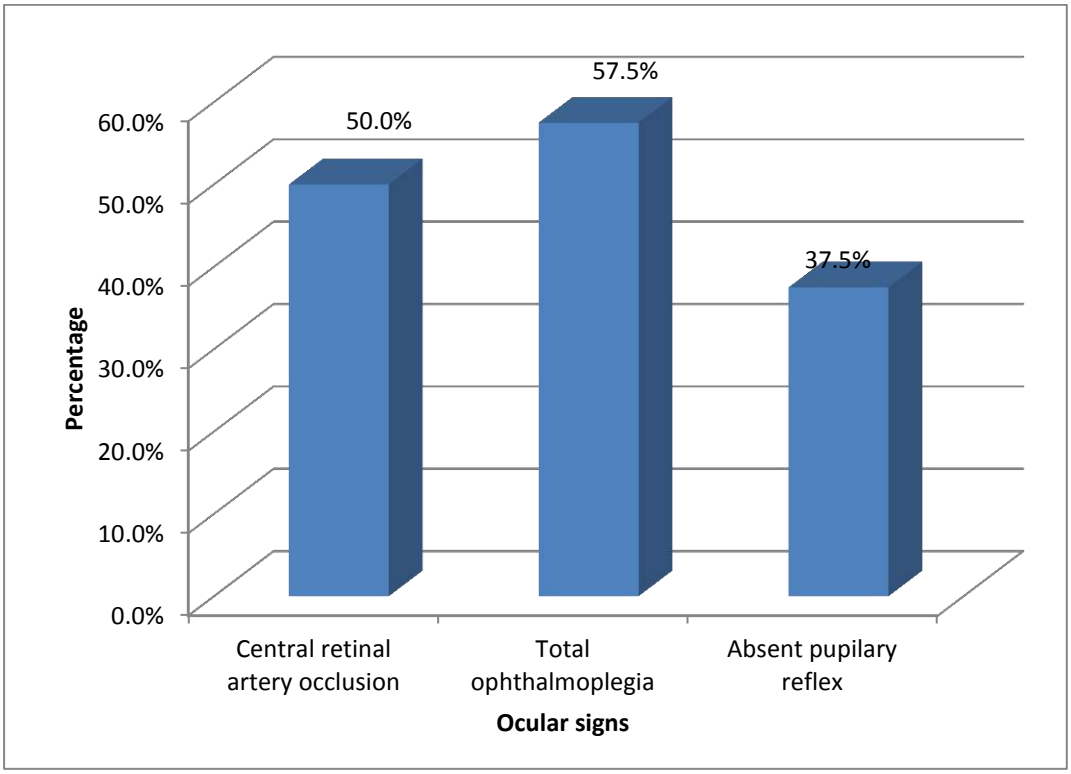
n=total number of patients %=percentage of patients

Total ophthalmoplegia was present in 57.5% of the patients and central retinal artery occlusion in 50 % of the patients on fundus examinationand absent pupillary reflex was absent in 37.5 % of the patients in our study.

FIGURE -XXX

OCULAR SIGNS

(n=40)



Total ophthalmoplegia was present in 57.5% of the patients with central retinal artery occlusion in 50 % of the patients on fundus examination and absent pupillary reflex was absent in 37.5 % of the patients in our study.

TABLE-XXXI

OPHTHALMIC EXAMINATION

(n=40)

Ophthalmic examination	No. of patients	% of patients
Chemosis	25	62.5%
Extra Ocular Muscle involvement	26	65.0%
Central Retinal Artery Occlusion	20	50.0%

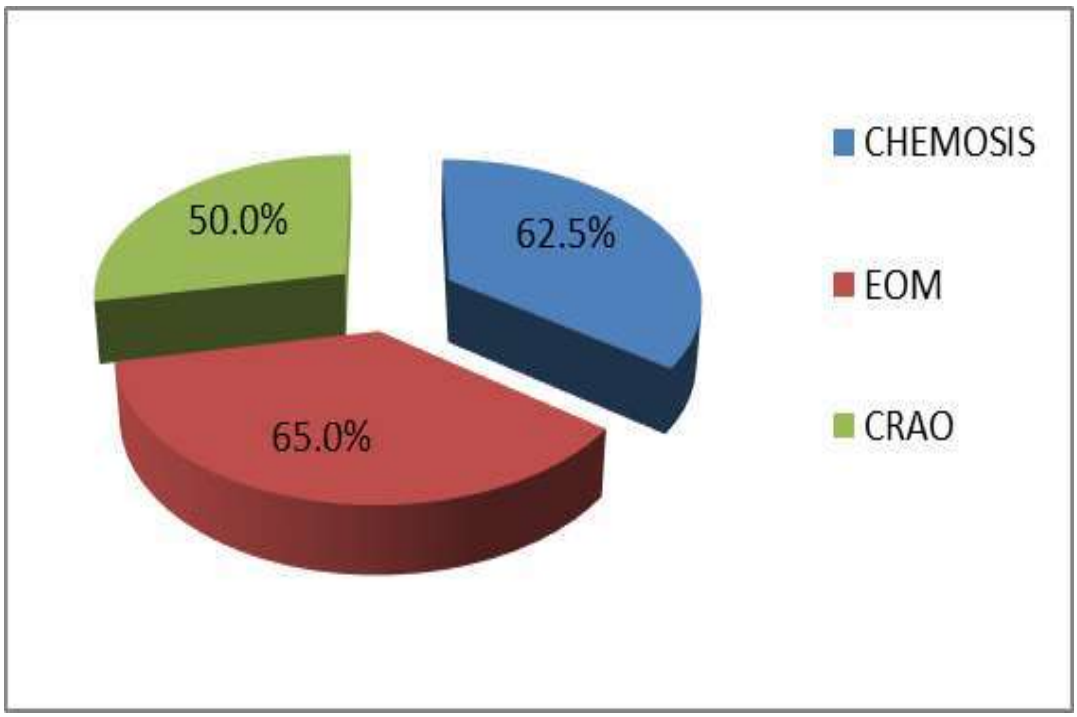
n=total number of patients %=percentage of patients

Extraocular muscle involvement (65%) was the most common finding on ophthalmic examination followed by chemosis (62.5%) in our study.

FIGURE-XXXI

OPHTHALMIC EXAMINATION

(n=40)



Extraocular muscle involvement (65%) was the most common finding on ophthalmic examination followed by chemosis (62.5%) in our study.

TABLE-XXXII

LATERALITY OF EYE INVOLVEMENT

(n=28)

Laterality of eye involvement	No. of patients	% of patients
RIGHT	9	32.1%
LEFT	19	67.9%
Total	28	100.0%

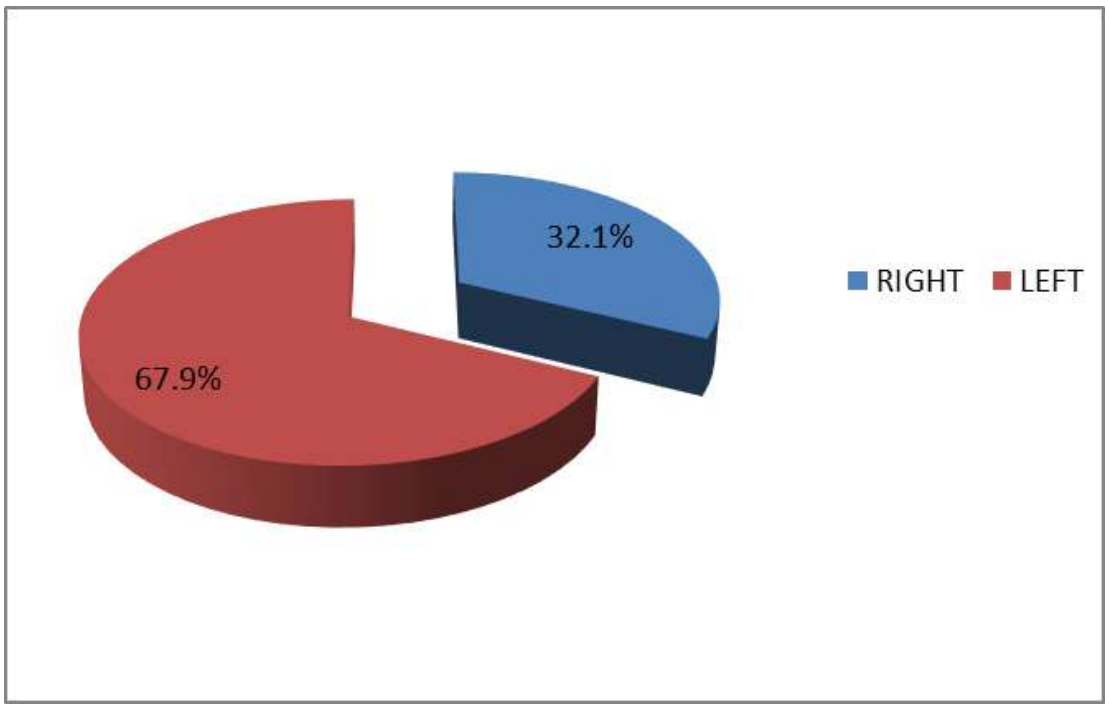
n=total number of patients %=percentage of patients

Left eye (67.9%) was predominantly involved in our study.

FIGURE-XXXII

LATERALITY OF EYE INVOLVEMENT

(n=28)



Left eye (67.9%) was predominantly involved in our study.

F) NEUROLOGICAL PROFILE

TABLE- XXXIII

NEUROLOGICAL INVOLVEMENT

(n=40)

Neurological Involvement	No of patients	% of patients
Cranial nerve involvement	34	85.0%
Cerebral involvement	8	20.0%
Cavernous sinus involvement	2	5.0%

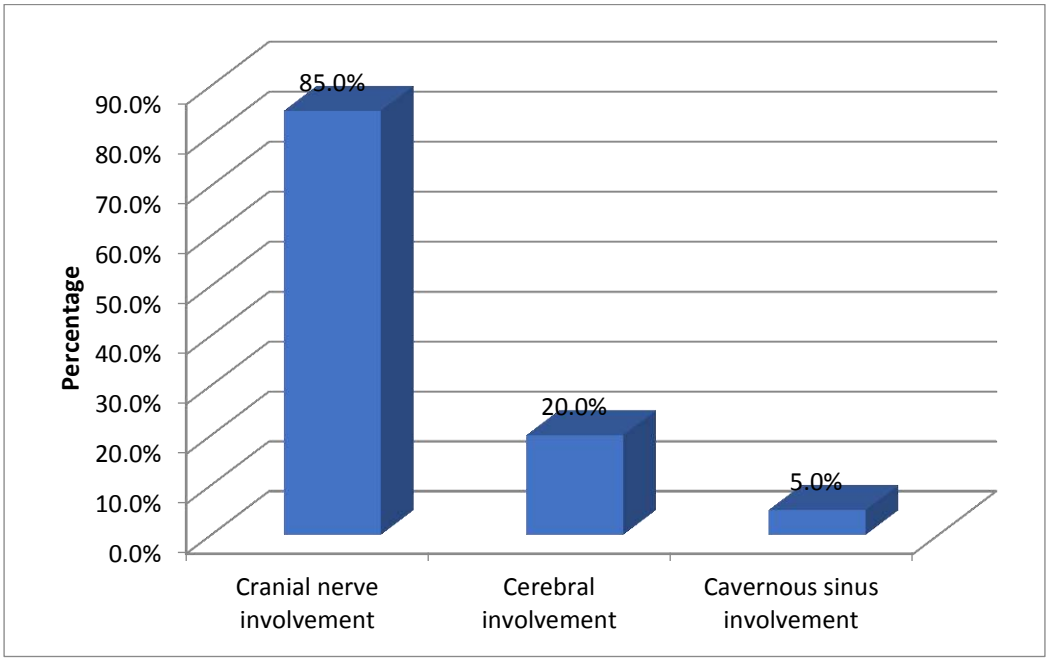
n=total number of patients %=percentage of patients

Cranial nerve involvement was seen in 85% of the patients followed by cerebral involvement in 20% and cavernous sinus in 5% of the patients in our study.

FIGURE- XXXIII

NEUROLOGICAL INVOLVEMENT

(n=40)



Cranial nerve involvement was seen in 85% of the patients followed by cerebral involvement in 20% and cavernous sinus in 5% of the patients in our study.

TABLE-XXXIV

CRANIAL NERVE INVOLVEMENT

(n=40)

Cranial nerve examination	No. of patients	% of patients
II	18	45.0%
III	26	65.0%
IV	26	65.0%
V	21	52.5%
VI	28	70.0%
VII	5	12.5%

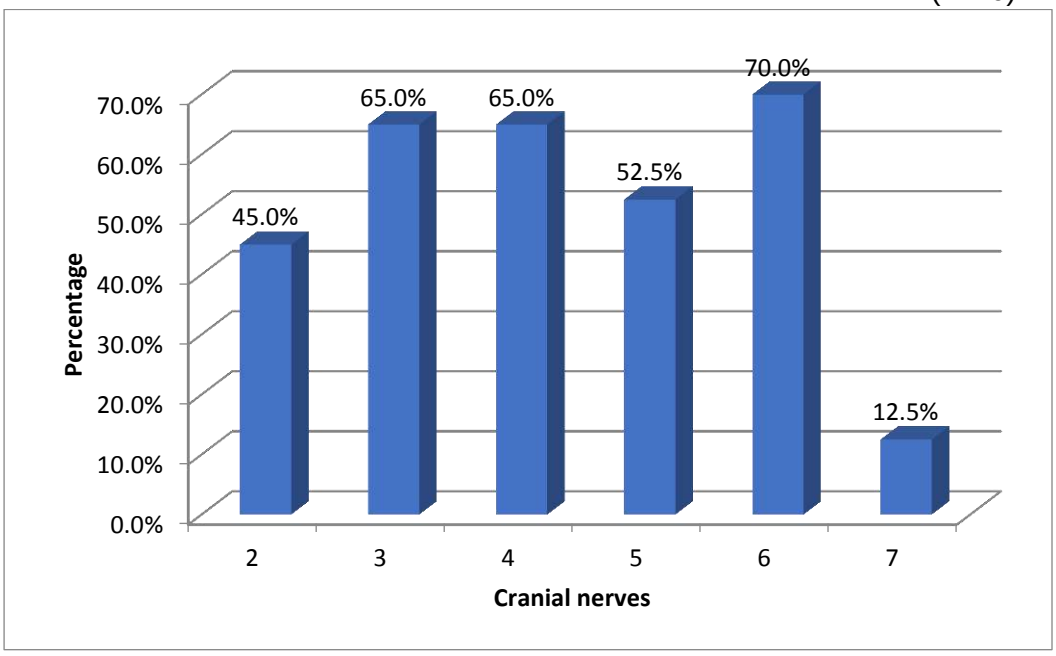
n=total number of patients %=percentage of patients

VI thcranial nerve (abducent) with lateral rectus palsy was the most common cranial nerve involved in our study.

FIGURE-XXXIV

CRANIAL NERVE INVOLVEMENT

(n=40)



Abducent /6 th cranial nerve was the most common cranial nerve involved in our study.

G) IMAGING STUDY PROFILE

TABLE-XXXV

SITE OF INVOLVEMENT ON COMPUTED TOMOGRAPHY/ MAGNETIC RESONANCE IMAGING

(n=40)

Site of involvement	No of patients	% of patients
Pranasal sinuses	40	100.0%
Extra Sinus	14	35.0%
Orbit	18	45.0%

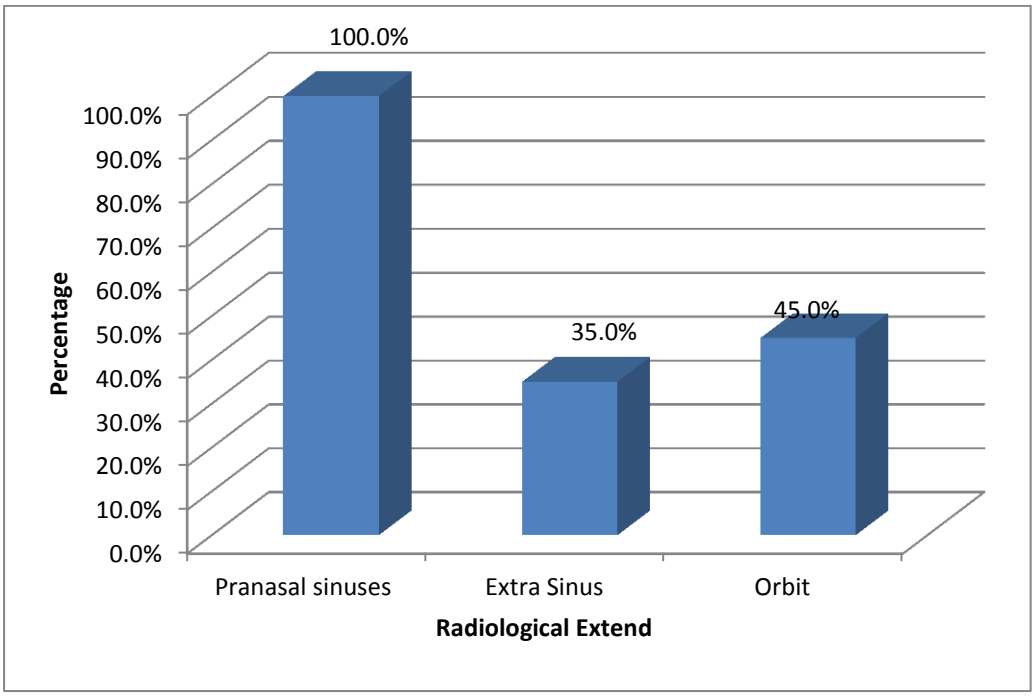
n=total number of patients %=percentage of patients

Paranasal sinuses were involved in all the patients while orbital involvement in 45 % of the patients with other extra sinus involvement in 35 % of the patients

FIGURE-XXXV

SITE OF INVOLVEMENT ON COMPUTED TOMOGRAPHY/ MAGNETIC RESONANCE IMAGING

(n=40)



Paranasal sinuses were involved in all the patients while orbital involvement in 45 % of the patients with other extra sinus involvement in 35 % of the patients.

TABLE-XXXVI

SINUS INVOLVEMENT ON COMPUTED TOMOGRAPHY

(n=40)

Paranasal Sinus	No. of patients	% of patients
Maxillary	39	97.5%
Ethmoid	38	95.0%
Frontal	31	77.5%
Sphenoid	35	87.5%

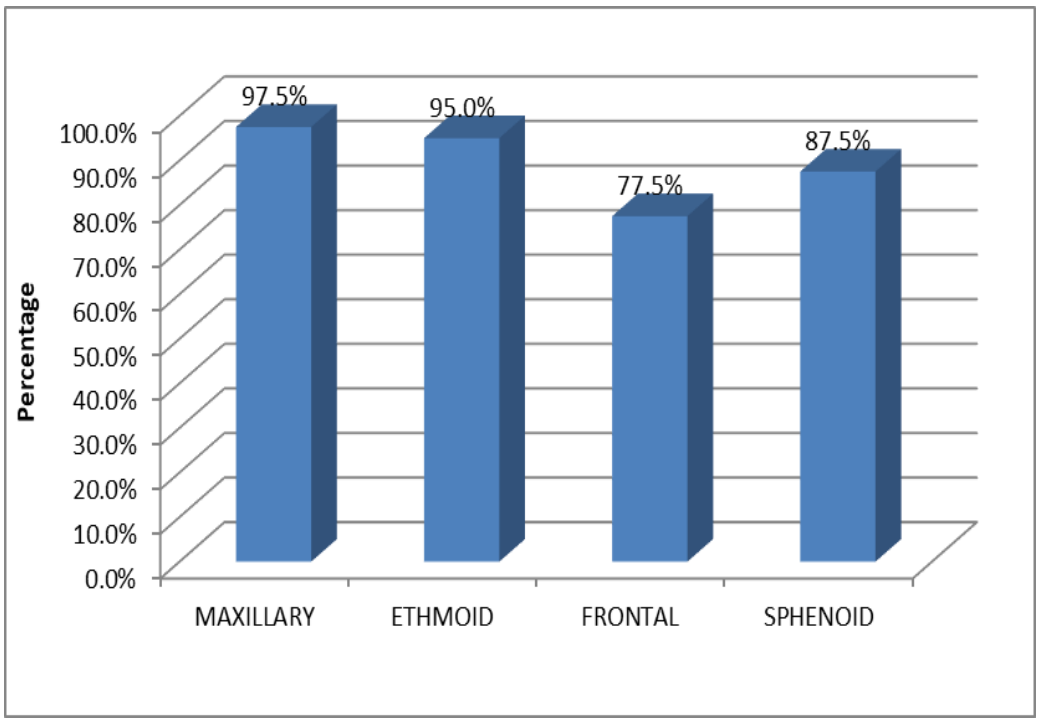
n=total number of patients %=percentage of patients

Maxillary sinus (97.5%) was the most common sinus involved followed by ethmoid sinus (95%) in our study.

FIGURE-XXXVI

SINUS INVOLVEMENT ON CT

(n=40)



Maxillary sinus (97.5%) was the most common sinus involved followed by ethmoid sinus (95%) in our study.

TABLE -XXXVII

COMPUTED TOMOGRAPHIC FINDINGS OF PARANASAL SINUSES

(n=40)

Paranasal sinus involvement	No of patients	% of patients
Mucosal Thickening	17	42.5%
Sinus wall destruction/ Bony Erosion	7	17.5%
Hyperdensity/ Opacification	23	57.5%
Total number of patients	40	100%

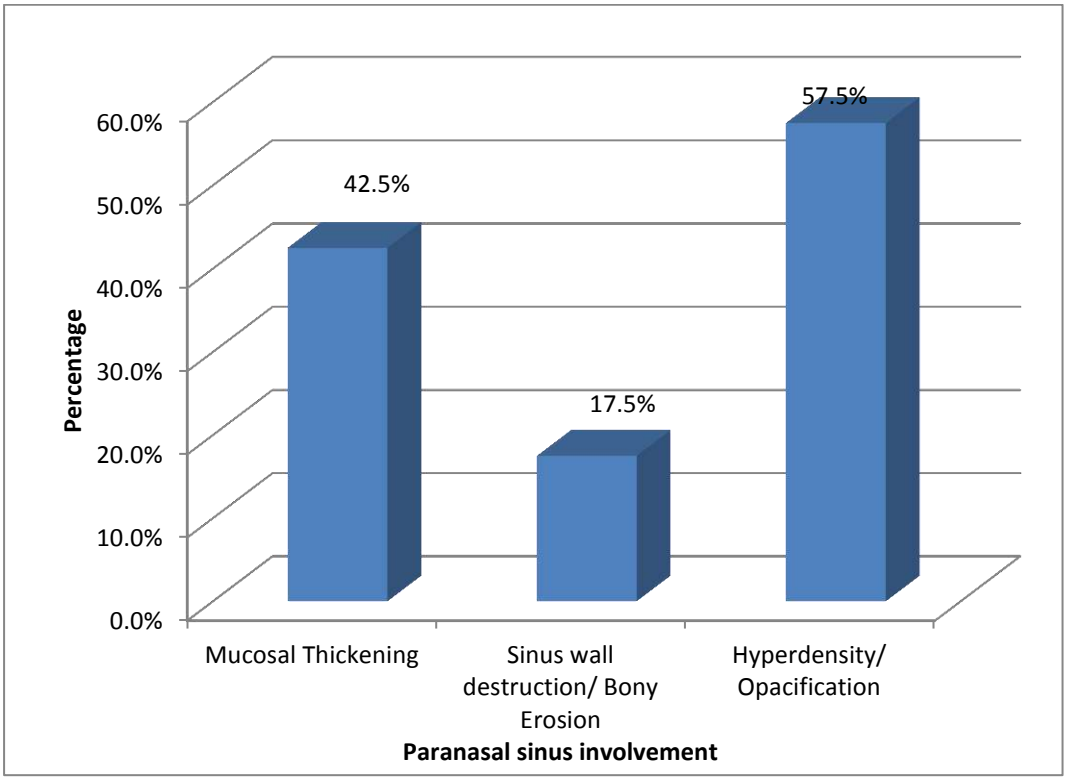
n=total number of patients %=percentage of patients

Paranasal sinus opacification was present in 57.5 % of the patients followed by mucosal thickening in 42.5% of the patients and bone erosion in 17.5 % of the patients.

FIGURE-XXXVII

COMPUTED TOMOGRAPHIC FINDINGS OF PARANASAL SINUSES

(n=40)



Paranasal sinus opacification was present in 57.5 % of the patients followed by mucosal thickening in 42.5% of the patients and bone erosion in 17.5 % of the patients.

TABLE- XXXVIII

EXTRA SINUS SITE INVOLVEMENT ON COMPUTED TOMOGRAPHY/MAGNETIC RESONANCE IMAGING

(n=14)

Extra sinus site	No of patients	% of patients
Nasolacrimal duct	1	7.1%
Infra Temporal fossa	9	64.3%
Perineural involvement	5	35.7%
Perivascular involvement	1	7.1%

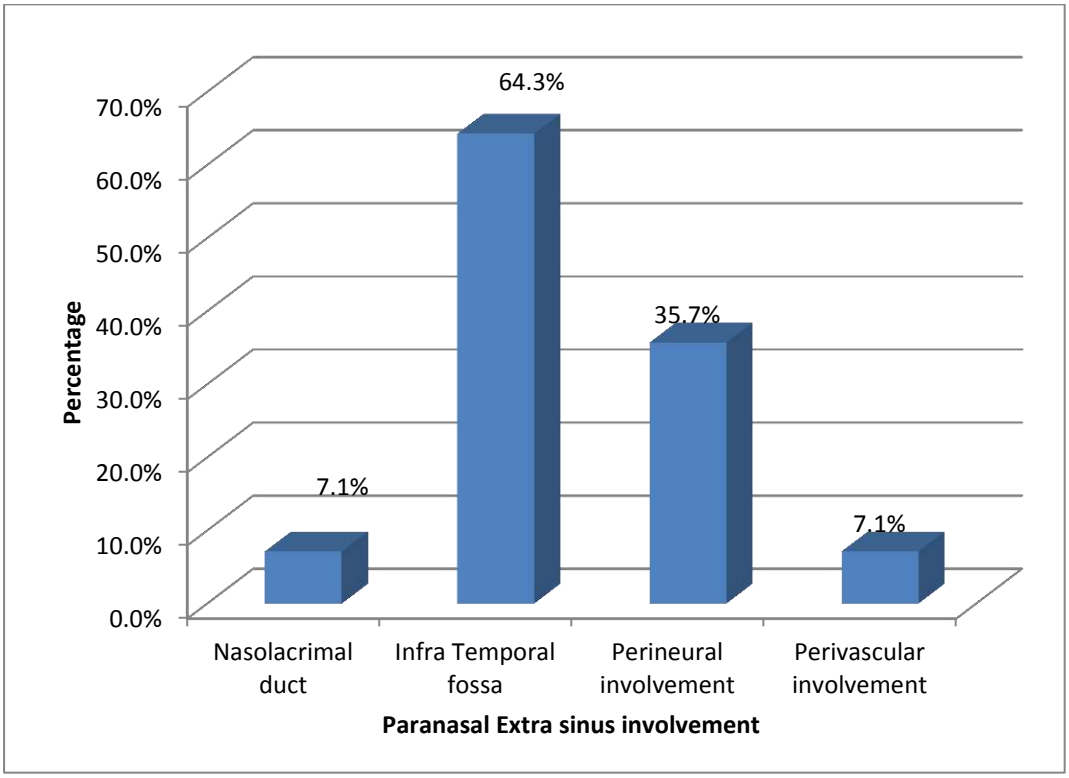
n=total number of patients %=percentage of patients

Infratemporal fossa was the most common extra sinus site (64.3%) involved

FIGURE-XXXVIII

EXTRA SINUS SITE INVOLVEMENT ON COMPUTED TOMOGRAPHY/MAGNETIC RESONANCE IMAGING

(n=14)



Infratemporal fossa was the most common extra sinus site (64.3%) involved

TABLE-XXXIX

ORBITAL INVOLVEMENT ON COMPUTED TOMOGRAPHY

(n=18)

Orbit	No of patients	Percentage
Proptosis	8	44.4%
Preseptal cellulitis	4	22.2%
Orbital cellulitis	14	77.8%

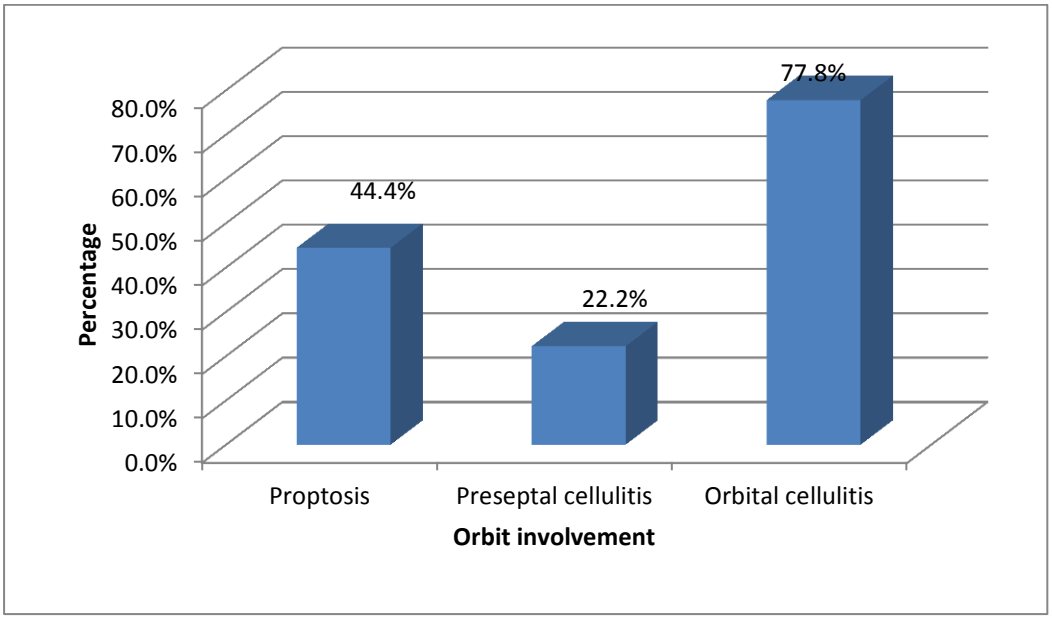
n=total number of patients %=percentage of patients

Orbital cellulitis was present in 77.8 % of the patients with orbital involvement while proptosis in 44.4 % of the patients with orbital involvement.

FIGURE -XXXIX

ORBITAL INVOLVEMENT ON COMPUTED TOMOGRAPHY

(n=18)



Orbital cellulitis was present in 77.8 % of the patients with orbital involvement while proptosis in 44.4 % of the patients with orbital involvement.

TABLE-XXXX

LATERALITY OF ORBITAL INVOLVEMENT

(n=18)

Laterality of orbital involvement	No. of patients	% of patients
Left	13	72.2%
Right	5	27.8%
Total number of patients	18	100%

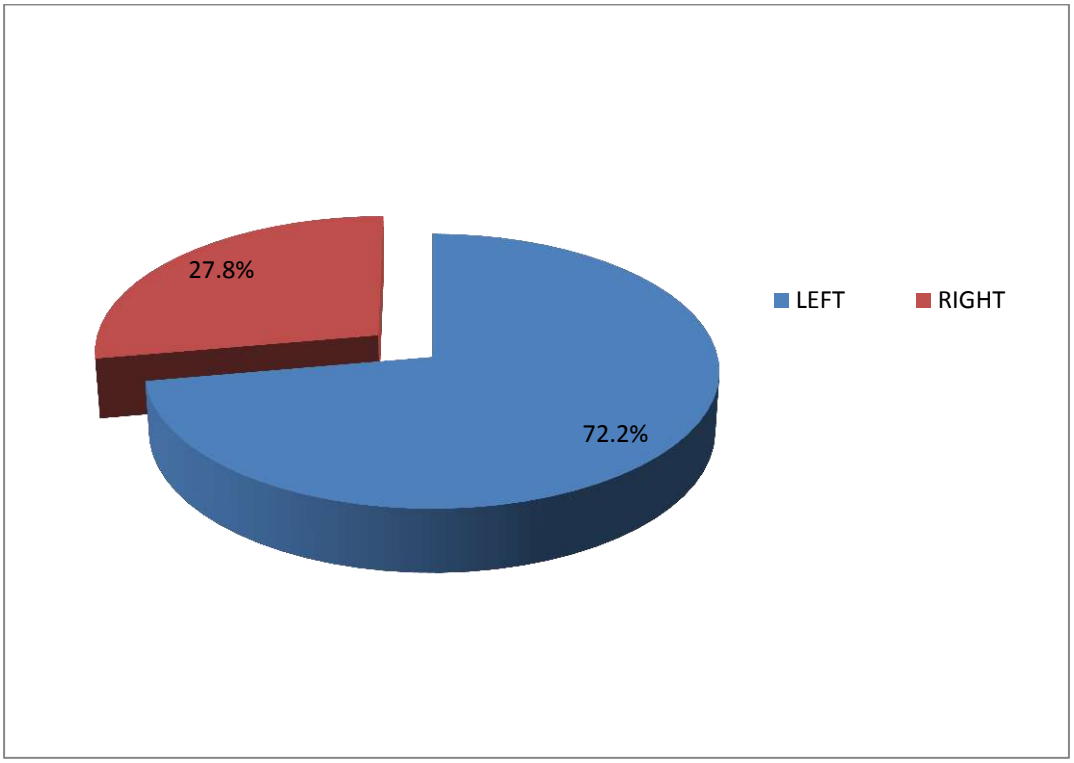
n=total number of patients %=percentage of patients

Left sided (71.4%) orbital involvement was predominant in our study.

FIGURE-XXXX

LATERALITY OF ORBITAL INVOLVEMENT

(n=18)



Left sided (71.4%) orbital involvement was predominant in our study.

TABLE-XXXXI

SUMMARY OF RADIOLOGICAL FINDINGS

(n=40)

Feature	No of patients	% of patients
Paranasal sinus Mucosal Thickening	17	42.5%
Paranasal Sinus wall destruction/ Bony Erosion	7	17.5%
Paranasal sinus hyperdensity/ Opacification	23	57.5%
Nasolacrimal duct involvement	1	2.5%
Infra Temporal fossa involvement	9	22.5%
Perineural involvement	5	12.5%
Perivascular involvement	1	2.5%
Proptosis	8	20.0%
Preseptal cellulitis	4	10.0%
Orbital cellulitis	14	35.0%

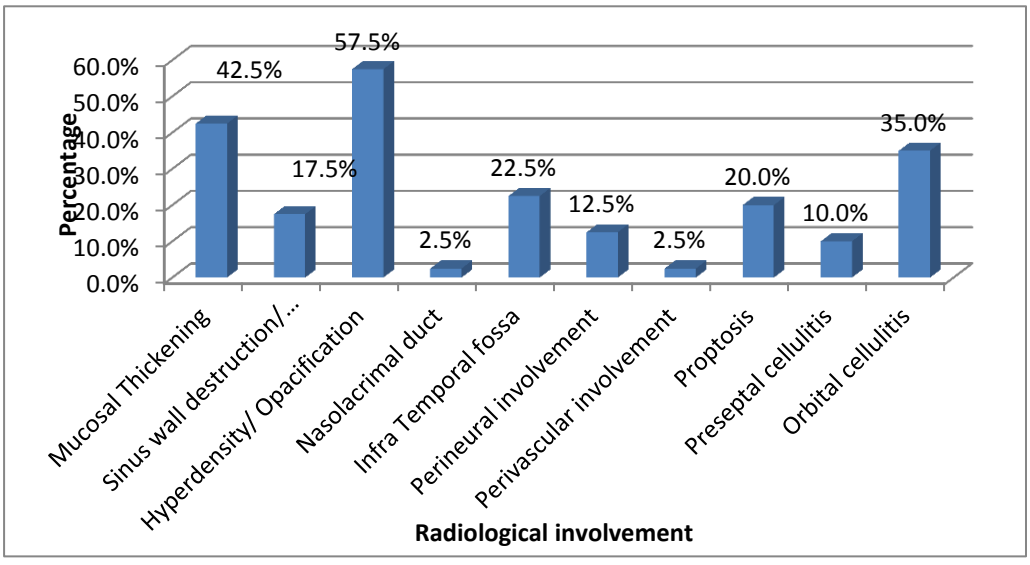
n=total number of patients %=percentage of patients

Paranasal sinus opacification (57.5%) was the most common radiological finding followed by paranasal sinus mucosal thickening (42.5%) in our study.

FIGURE-XXXXI

SUMMARY OF RADIOLOGICAL FINDINGS

(n=40)



Paranasal sinus opacification (57.5%) was the most common radiological finding followed by paranasal sinus mucosal thickening (42.5%) in our study

TABLE-XXXXII

STATUS OF NASAL SEPTUM

(n=40)

Septum	No. of patients	% of patients
Deviated nasal septum left	8	20.0%
Deviated nasal septum right	17	42.5%
Straight	15	37.5%
Totalnumber of patients	40	100.0%

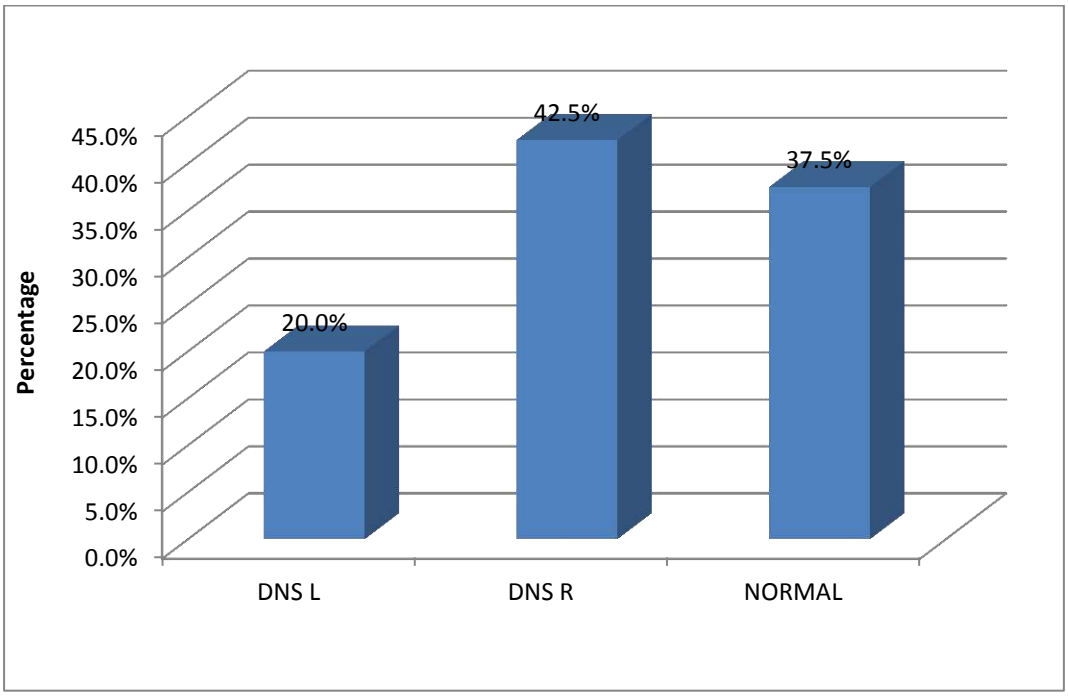
n=total number of patients %=percentage of patients

Deviated nasal septum of right side was present in 42.5% of the patients in our study.

FIGURE-XXXXII

STATUS OF NASAL SEPTUM

(n=40)



Deviated nasal septum of right side was present in 42.5% of the patients in our study

H) MYCOLOGICAL PROFILE

TABLE- XXXXIII

COMPARISON OF HISTOPATHOLOGY/KOH/FUNGAL CULTURE POSITIVITY

(n=40)

Investigation undertaken	No of patients	% of patients
KOH Examination(n=31)	19	61.3%
Fungal culture(n=29)	5	17.2%
Histopathological examination(n=40)	40	100.0%

n=total number of patients %=percentage of patients

Out of 40 patients, HPE was done in all while fungal smear KOH and fungal culture in 31 and 29 patients.

All the patients (100%) were diagnosed as cases of zygomycoses on histopathological examination of the debrided tissue.

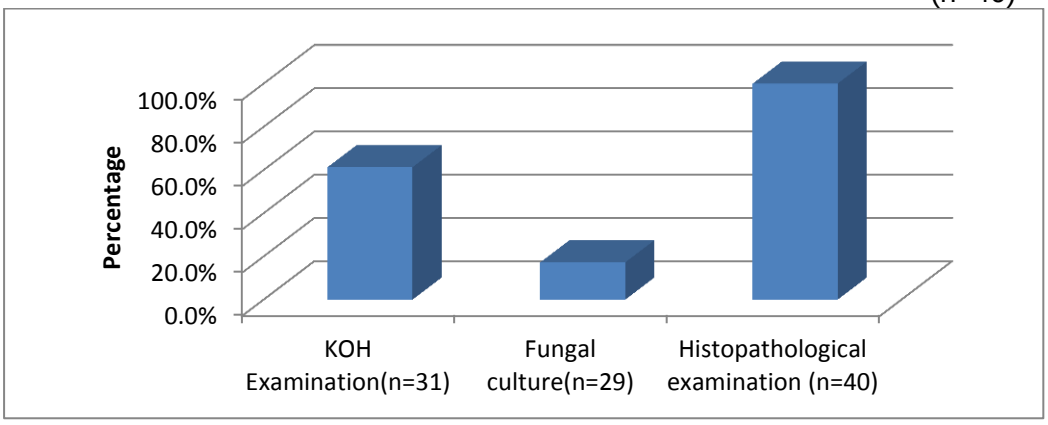
Koh examination showed aseptate hyphae in 61.3 % (19) of the patients.

Fungal culture isolates from the involved tissue showed growth of mucor in 5 (17.2%) patients.

FIGURE- XXXXIII

COMPARISON OF HISTOPATHOLOGY/KOH/FUNGAL CULLTURE POSITIVITY

(n=40)



All the patients (100%) were diagnosed as cases of zygomycoses on histopathological examination of the debrided tissue.

Koh examination showed aseptate hyphae in 47.5 % (19) of the patients

Fungal culture isolates from the involved tissue showed growth of mucor in 5 (12.5%) patients.

TABLE-XXXXIV

TYPE OF HYPHAE ON KOH EXAMINATION

(n=31)

Koh examination	No. of patients	% of patients
Septate hyphae	12	38.7%
Aseptate hyphae	19	61.3%

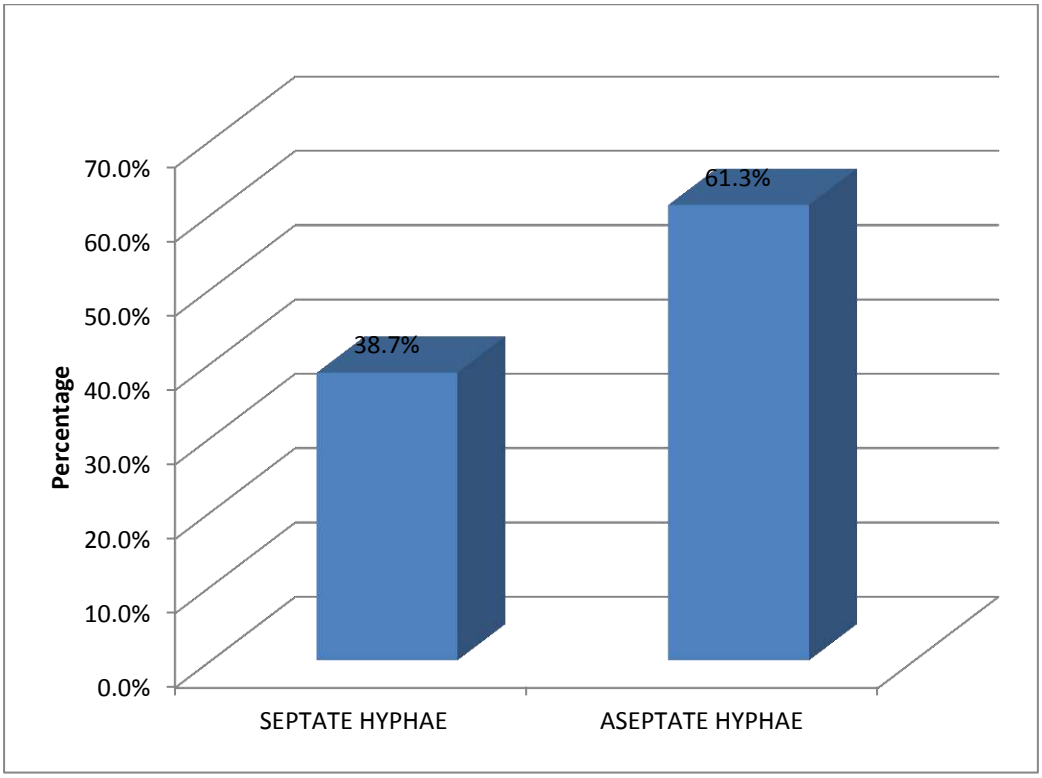
n=total number of patients %=percentage of patients

Aseptate hyphae were present in 61.3 % of the patients while septate in 38.7% of the patients in our study.

FIGURE-XXXXIV

TYPE OF HYPHAE ON KOH EXAMINATION

(n=31)



Aseptate hyphae were present in 61.3% of the patients while septate in 38.7% of the patients in our study.

TABLE-XXXXV

GROWTH ON FUNGAL CULTURE

(n=29)

Fungal culture	No. of patients	% of patients
Aspergillus flavus	8	27.6%
Mucor	5	17.2%
No growth	15	55.2%

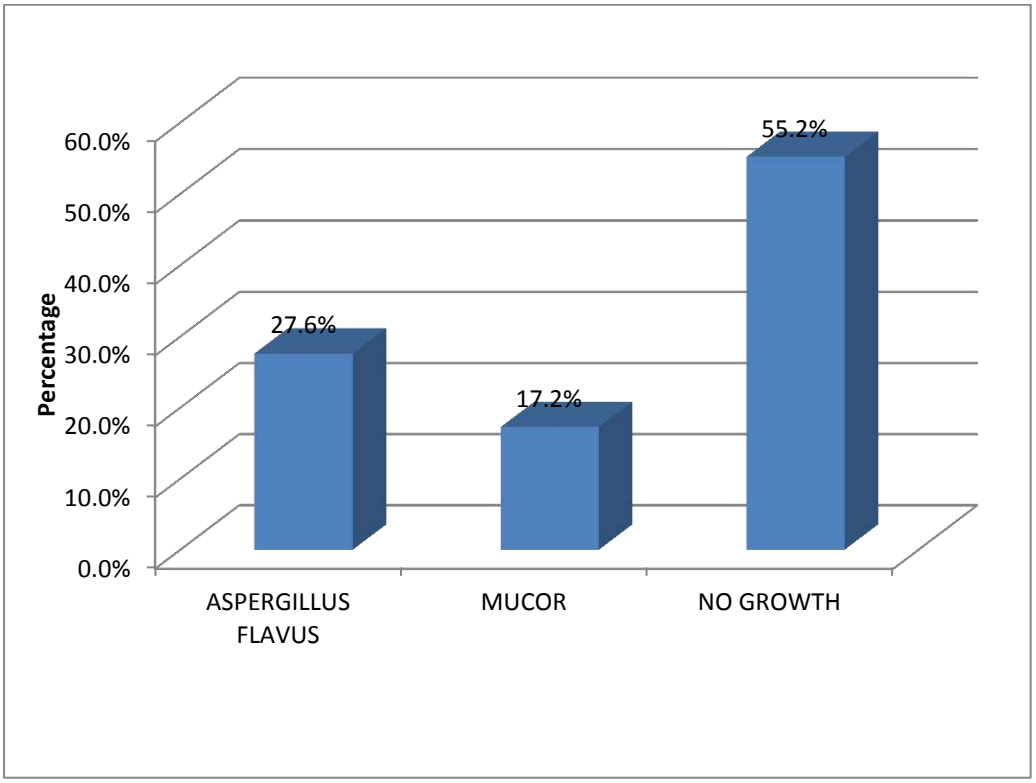
n=total number of patients %=percentage of patients

Growth of mucor was observed in 17.2% of the patients, in 27.6% Aspergillus flavus was obtained .

FIGURE-XXXXV

GROWTH ON FUNGAL CULTURE

(n=29)



Growth of mucor was observed in 17.2% of the patients, in 27.6% Aspergillus flavus was obtained.

TABLE- XXXXVA

COMPARISON OF FUNGAL SMEAR AND CULTURE

(n=29)

		FUNGAL CULTURE-MUCOR				Total	chi-square value	p-value
		Positive		Negative				
Koh examination	positive	4	80.0%	13	54.2%	17	1.1384	0.286
	Negative	1	20.0%	11	45.8%	12		
Total		5	100.0%	24	100.0%	29		

n=total number of patients %=percentage of patients

Both fungal smear KOH and fungal culture were positive in 4 patients.p value 0.286

Sensitivity of fungal smear KOH was 80% and specificity 45.83% as compared to fungal culture.

Statistic	Value	95% CI
Sensitivity	80.00%	28.36% to 99.49%
Specificity	45.83%	25.55% to 67.18%
Positive Likelihood Ratio	1.48	0.83 to 2.62
Negative Likelihood Ratio	0.44	0.07 to 2.66
Disease prevalence	17.24% (*)	5.85% to 35.77%
Positive Predictive Value	23.53% (*)	14.79% to 35.29%
Negative Predictive Value	91.67 % (*)	64.37% to 98.53%
Accuracy	51.72% (*)	32.53% to 70.55%

I) MEDICAL THERAPEUTICS

TABLE-XXXXVI

TYPE OF AMPHOTERICIN B ADMINISTRATION

(n=39)

Type of amphotericin B	No. of patients	% of patients
Amphotericin b conventional	17	43.6%
Amphotericin b liposomal	22	56.4%
Total number of patients	39	100.0%

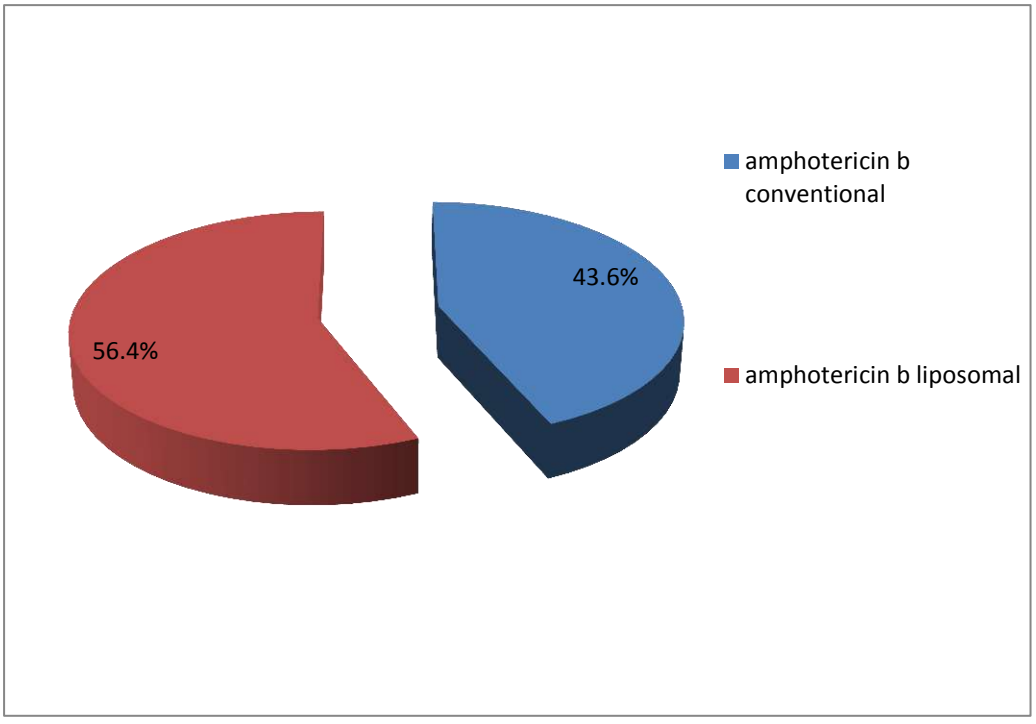
n=total number of patients %=percentage of patients

Amphotericin b was administered in all our patients except one who was not affording and went discharge against medical advise.

Liposomal amphotericin b was given in 56.4 % of the patients while conventional amphotericin b was given in 43.6 % of the patients in our study.

FIGURE-XXXXVI
TYPE OF AMPHOTERICIN B GIVEN

(n=39)



Liposomal amphotericin b was given in 56.4 % of the patients while conventional amphotericin b was given in 43.6 % of the patients in our study

TABLE-XXXXVII

DOSE OF AMPHOTERICIN B TITRATION

(n=39)

Amphotericin B DOSE	No. of patients	% of patients
<1gm	6	15.4%
1-2gm	13	33.3%
2-3gm	20	51.3%

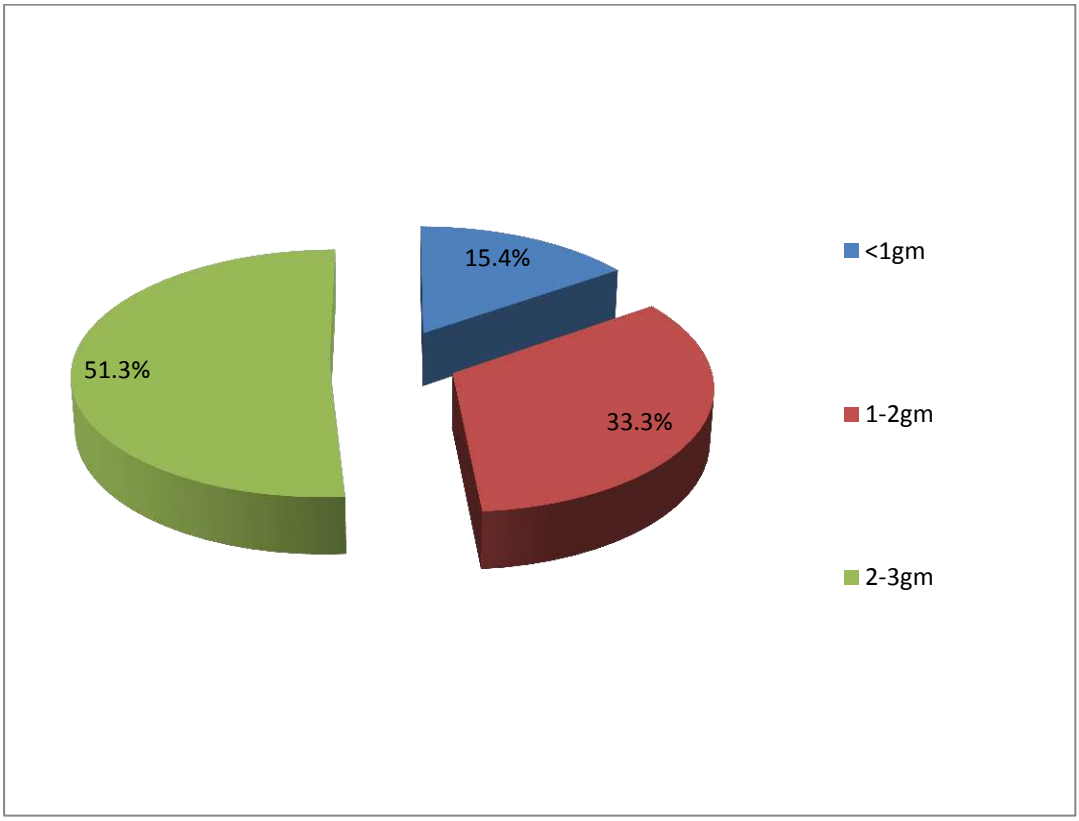
n=total number of patients %=percentage of patients

Amphotericin b was given in the dose of 2-3 gms in 51.3 % of the patients followed by 1-2gm in 33.3% of the patients in our study.

FIGURE-XXXXVII

DOSE OF AMPHOTERICIN B

(n=39)



Amphotericin b was given in the dose of 2-3 gms in 51.3 % of the patients followed by 1-2gm in 33.3% of the patients.

TABLE-XXXXVIII

POST AMPHOTERICIN ADMINISTRATION SERUM CREATININE VALUES

(n=39)

Creatinine(mg/dl)	No. of patients	% of patients
< 1.5	24	60.0%
1.5-2	4	10.0%
> 2	11	30.0%

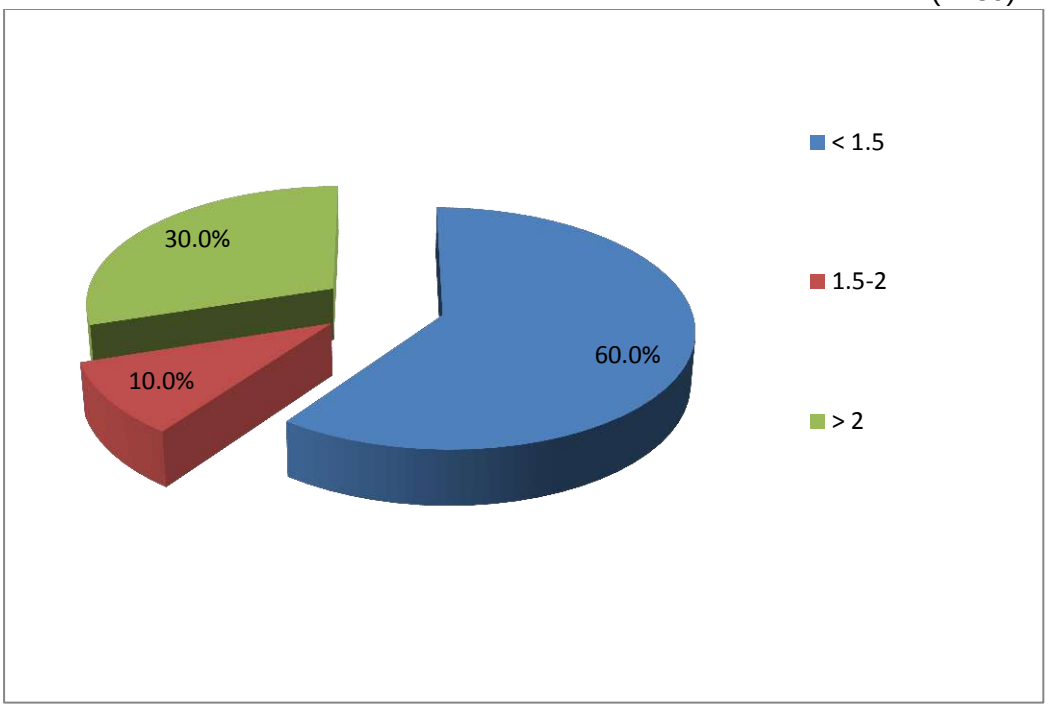
n=total number of patients %=percentage of patients

Serum creatinine values were less than1.5 gm/dl in 60% of the patients while it was more than 2 mg/dl in 30% of the patients.

TABLE-XXXXVIII

POST AMPHOTERICIN ADMINISTRATION SERUM CREATININE VALUES

(n=39)



Serum creatinine values were less than1.5 gm/dl in 60% of the patients while it was more than 2 mg/dl in 30% of the patients.

J) SURGICAL THERAPEUTICS

TABLE-XXXXIX

SURGICAL THERAPEUTICS

(n=40)

Surgical Therapeutics	No of patients	% of patients
Nasal debridement	40	100.0%
Orbital exenteration	6	15.0%
Maxillectomy	6	15.0%
Palatal debridement	7	17.5%

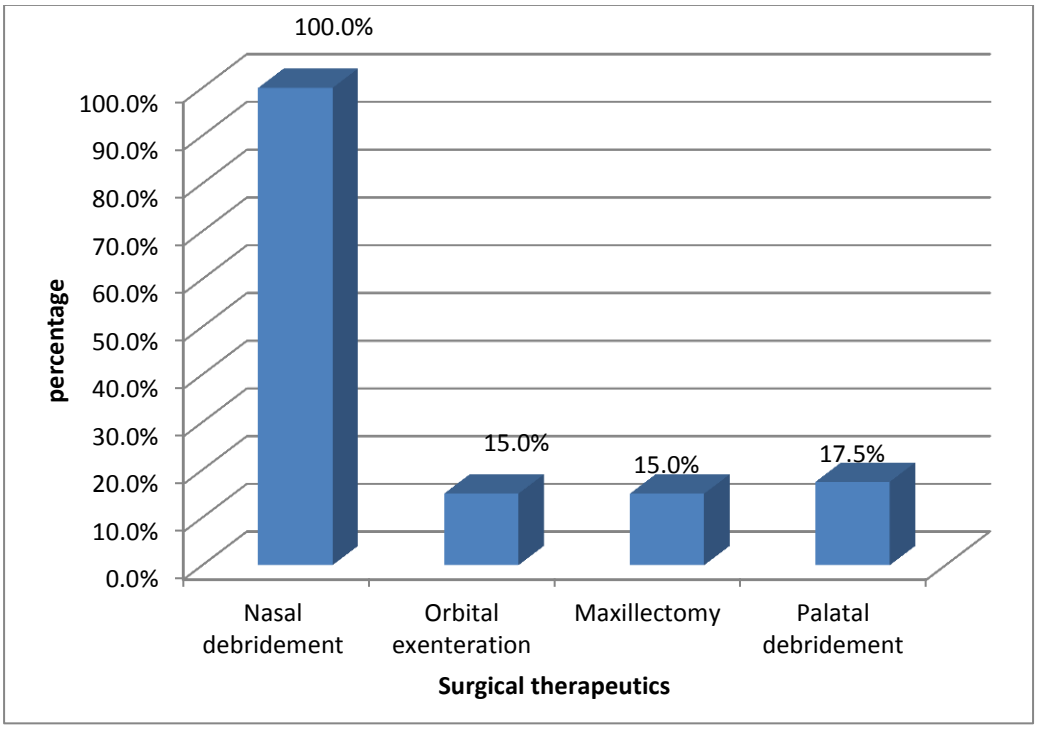
n=total number of patients %=percentage of patients

Nasal debridement (100%) was performed in all the patients followed by orbital exenteration (15%) and maxillectomy (15%) of the patients in our study.

FIGURE-XXXXIX

SURGICAL THERAPEUTICS

(n=40)



Nasal debridement (100%) was done in all the patients followed by orbital exenteration(15%) and maxillectomy (15%) of the patients in our study

TABLE-XXXXX

TYPE OF ANESTHESIA USED

(n=40)

Anesthesia	No. of patients	% of patients
General anesthesia	33	82.5%
Local Anaesthesia	3	7.5%
Minimum anestheticconcenteration	4	10.0%
Total number of patients	40	100.0%

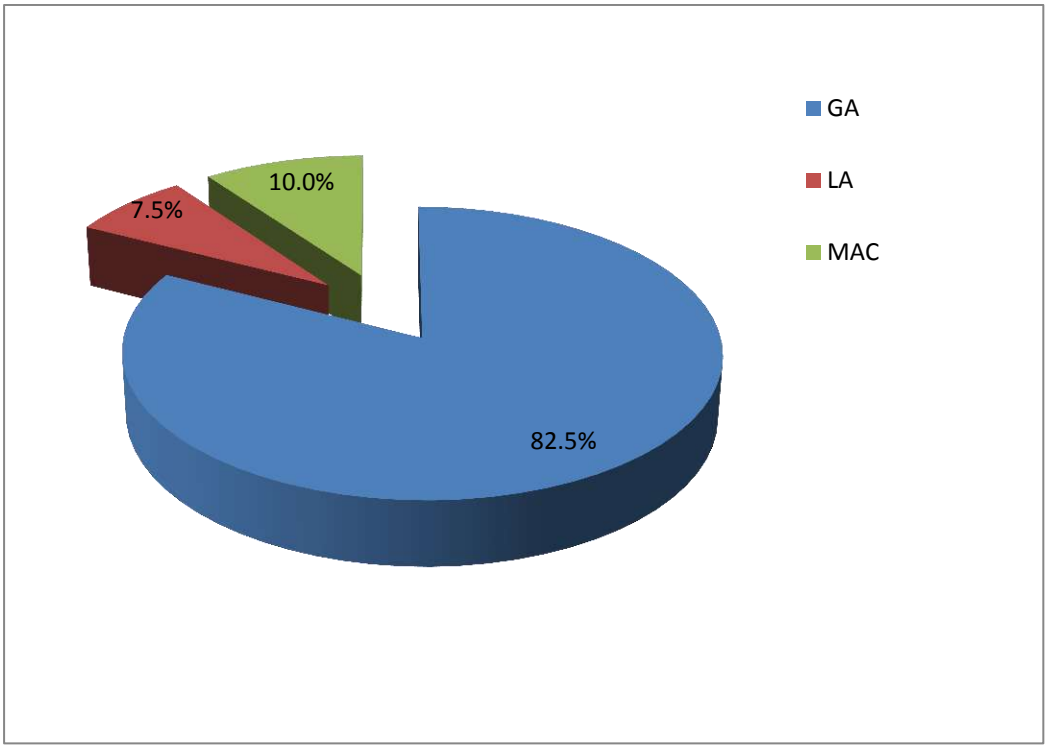
n=total number of patients %=percentage of patients

82.5 % of the patients were performed under GA (general anesthesia), followed by 10 % patients under MAC (minimal anesthetic concentration) followed by 7.5% under LA (local anesthesia).

FIGURE-XXXXX

TYPE OF ANESTHESIA USED

(n=40)



82.5 % of the patients were done under GA (general anesthesia), followed by 10 % patients under MAC (minimal anesthetic concentration) followed by 7.5% under LA (local anesthesia) .

TABLE- XXXXXI

PATIENT OUTCOME DURING HOSPITAL STAY

(n=40)

Patient outcome during hospital stay	No. of patients	% of patients
SURVIVED	36	90.0%
EXPIRED	4	10.0%

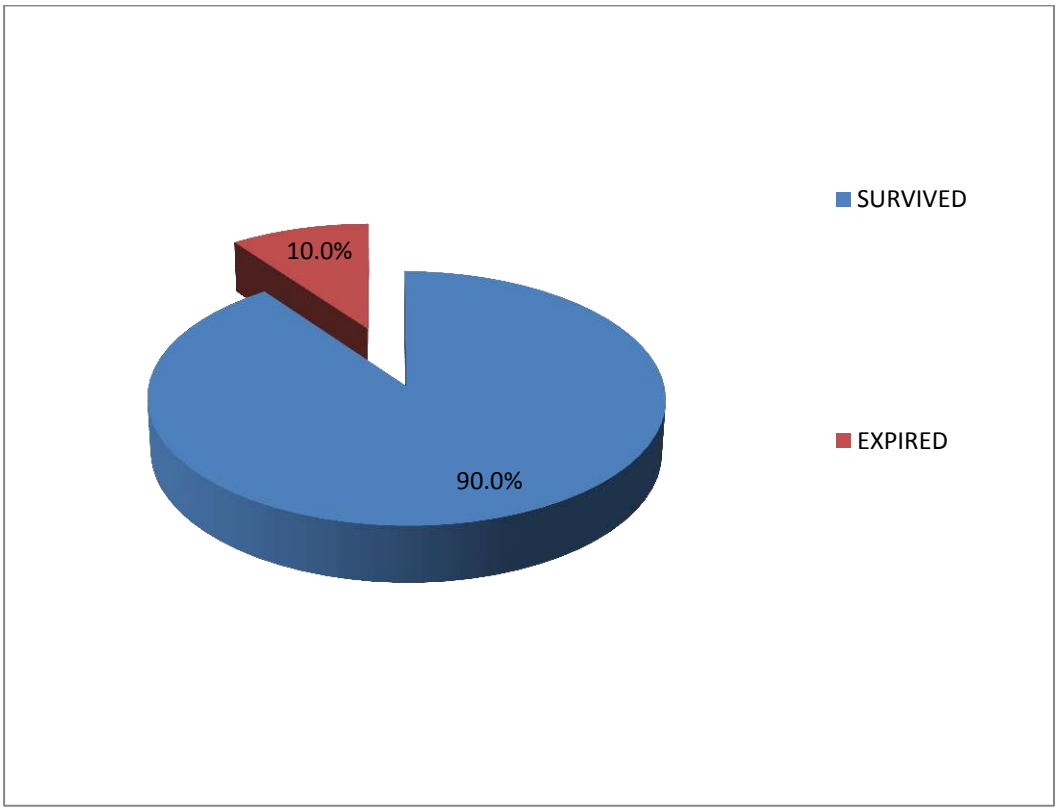
n=total number of patients %=percentage of patients

4 patients could not be salvaged while 36 patients were discharged under stable conditions

TABLE- XXXXXI

PATIENT OUTCOME DURING HOSPITAL STAY

(n=40)



4 patients could not be salvaged while 36 patients were discharged under stable conditions.

K) POST TREATMENT FOLLOW UP

TABLE-XXXXXII

FOLLOW UP FIRST MONTH

(n=36)

Follow up_ 1st month	No. of patients	% of patients
Lost to follow up	5	13.9%
followed	31	86.1%
Total number of patients	36	100.0%

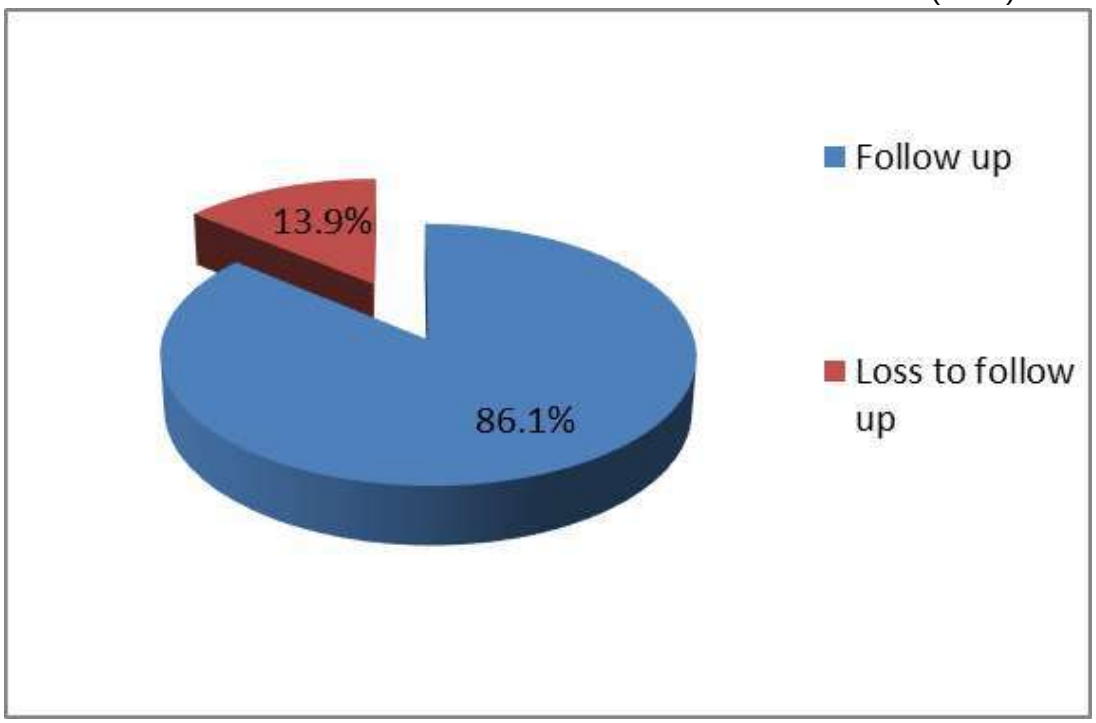
n=total number of patients %=percentage of patients

31 patients were followed up in first month and 5 patients did not turn up on follow up.

FIGURE -XXXXXII

FOLLOW UP FIRST MONTH

(n=36)



31 (86.1%)patients were followed up in first month while 5 (13.9%) patients did not turn up on follow up.

TABLE-XXXXXIII

FOLLOW UP THIRD MONTH

(n=36)

Follow up third month	No. of patients	% of patients
Lost to follow up	5	13.9%
On Follow up	31	86.1%
Total number of patients	36	100.0%

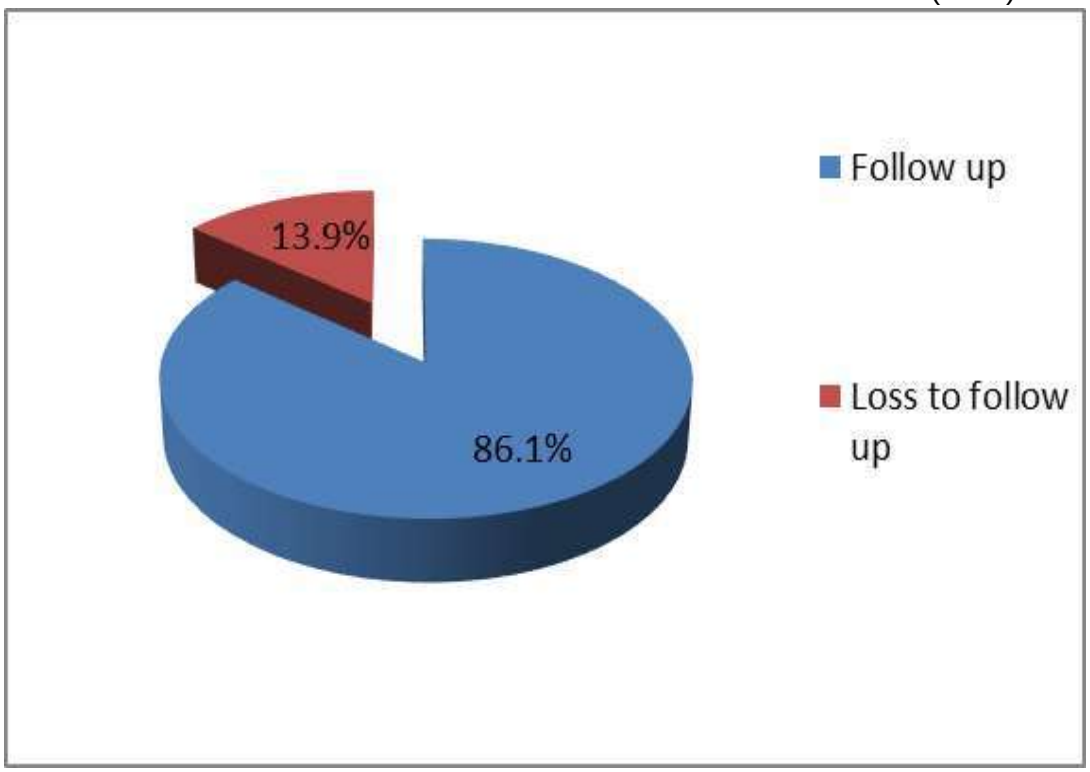
n=total number of patients %=percentage of patients

31 patients were followed up inthird month 5 patients did not turn up on follow up even on third month

FIGURE -XXXXXIII

FOLLOW UP THIRD MONTH

(n=36)



31 (86.1%) patients were followed up in third month while 5 (13.9%) patients did not turn up on follow up.

TABLE-XXXXXIV

FOLLOW UP SIXTH MONTH

(n=36)

Follow up sixth month	No. of patients	% of patients
Lost to follow up	5	13.9%
On follow up	31	86.1%%
Total number of patients	36	100.0%

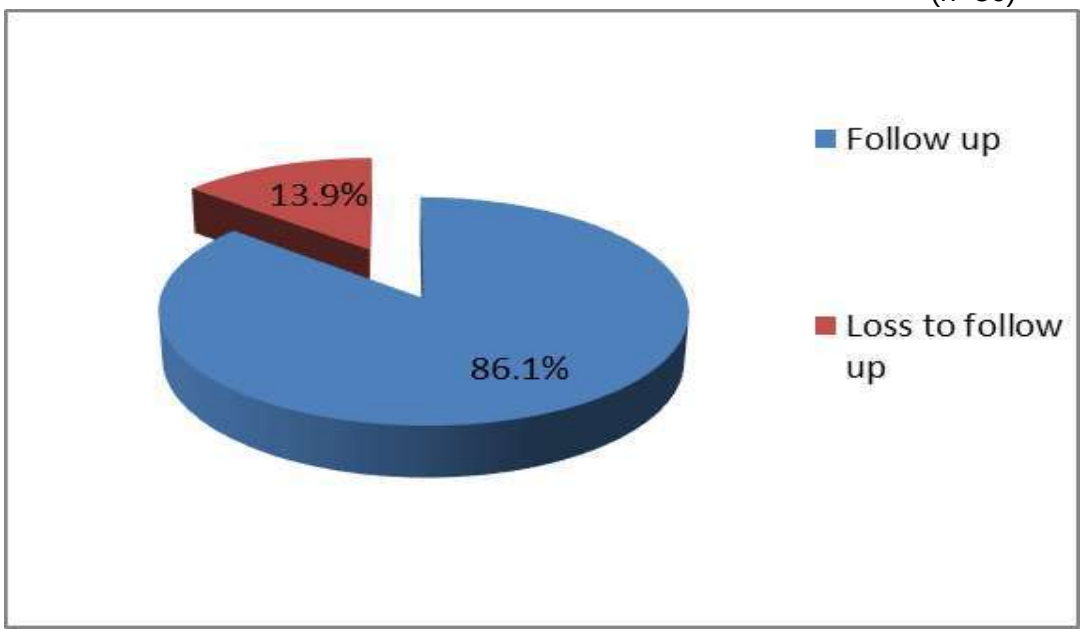
n=total number of patients %=percentage of patients

31 patients were followed up in sixth month follow up and 5 patients did not come up on follow up even on 6th month.

FIGURE -XXXXXIV

FOLLOW UP SIXTH MONTH

(n=36)

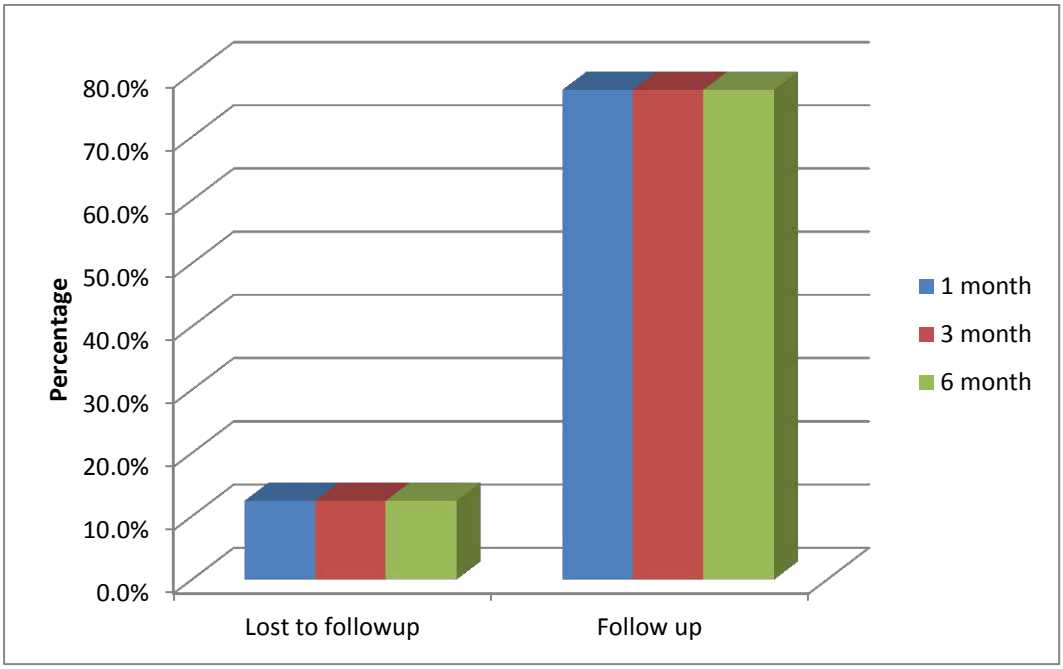


31 (86.1%) patients were followed up in sixth month while 5 (13.9%) patients did not turn up on follow up even on sixth month

FIGURE-XXXXXV

SUMMARY OF FOLLOW UP

(n=36)



31 patients were followed up for 6 months. 5 patients were lost to follow up .in our study.

L) OUTCOME

TABLE-XXXXXV

OUTCOME OF PATIENTS AT SIXTH MONTH FOLLOW UP

(n=40)

Outcome	No. of cases	
Loss to follow up	5	12.5%
Expired	4	10.0%
Survivor	31	77.5%
Total	40	100.0%

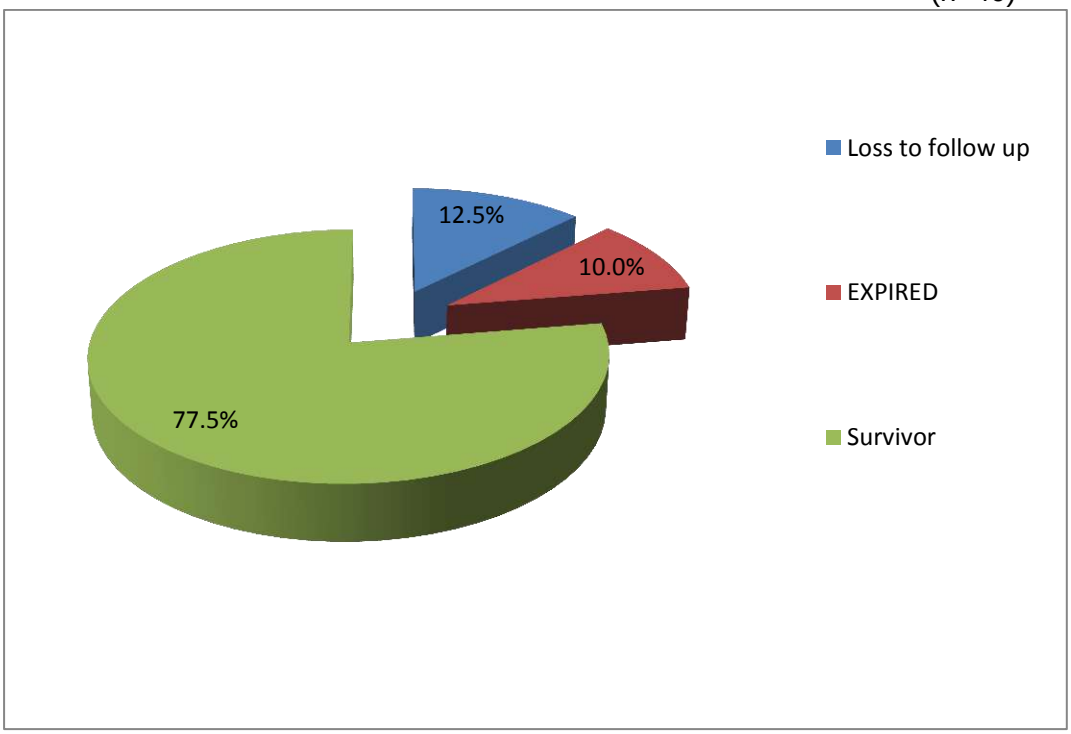
n=total number of patients %=percentage of patients

31 patients were survivors while in 4 patients outcome was unfavourable and 5 were lost to follow up thus survival rate in our study was 77.5 %.

FIGURE-XXXXXVI

OUTCOME OF PATIENTS AT SIXTH MONTH FOLLOW UP

(n=40)



There were 31 patients (77.5%) who could be salvaged while in 4 (10%) patients outcome was unfavourable.

M) OUTCOME ASSOCIATION

TABLE –XXXXXVI

AGE GROUP

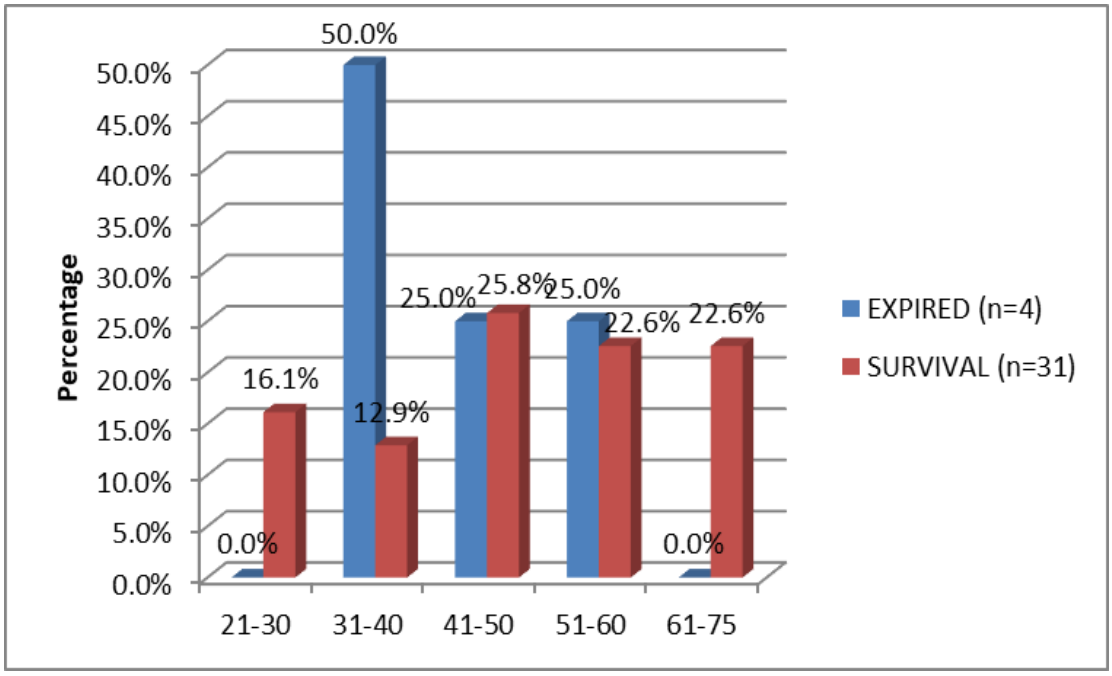
		OUTCOME				Total	Chi-square value	p-value
		EXPIRED (n=4)		SURVIVAL (n=31)				
Age group	21-30	0	0.0%	5	16.1%	5	4.402	0.354
	31-40	2	50.0%	4	12.9%	6		
	41-50	1	25.0%	8	25.8%	9		
	51-60	1	25.0%	7	22.6%	8		
	61-75	0	0.0%	7	22.6%	7		

n=total number of patients %=percentage of patients

Most patients who survived were in the age group 41-50 years.p value -0.345

FIGURE- XXXXXVII

AGE GROUP



Most patients who survived were in the age group 41-50 years.

TABLE –XXXXXVII

GENDER

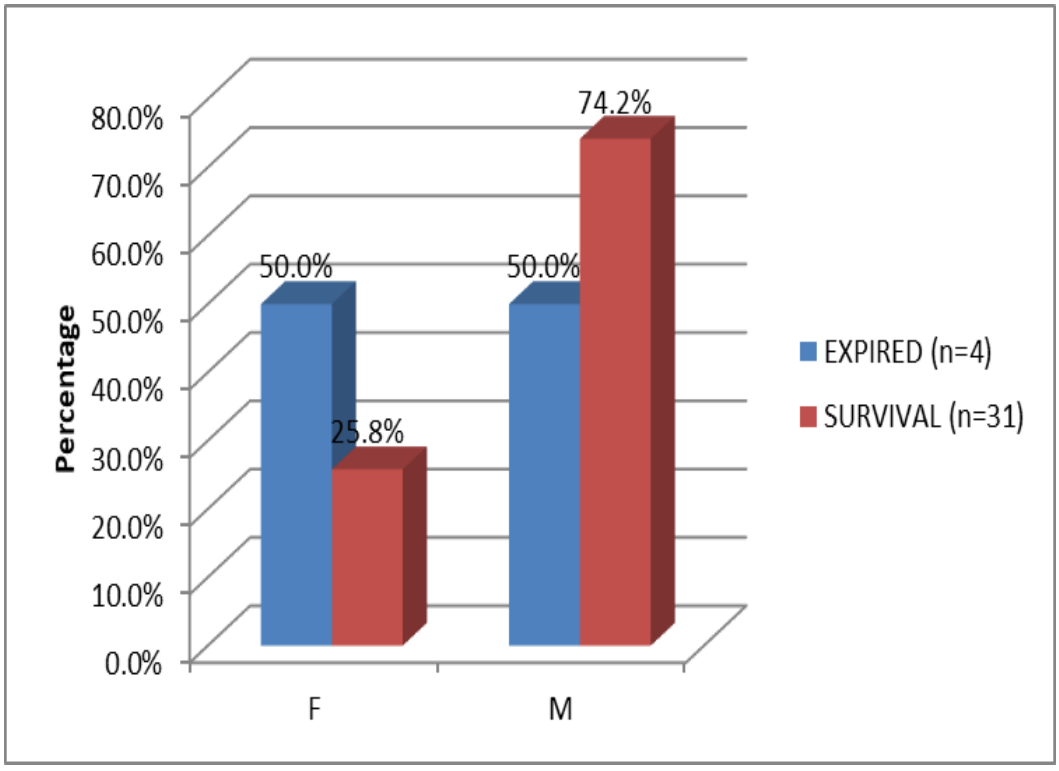
		OUTCOME				Total
		Expired (n=4)	**Expired (n=4)**	**Survival (n=31)**	**Survival (n=31)**	
Sex	F	2	50.0%	8	25.8%	10
	M	2	50.0%	23	74.2%	25

n=total number of patients %=percentage of patients

74.2% of the survivors were male in our study.

FIGURE- XXXXXVIII

GENDER



74.2% of the survivors were male in our study.

TABLE-XXXXXVIII

OCCUPATION

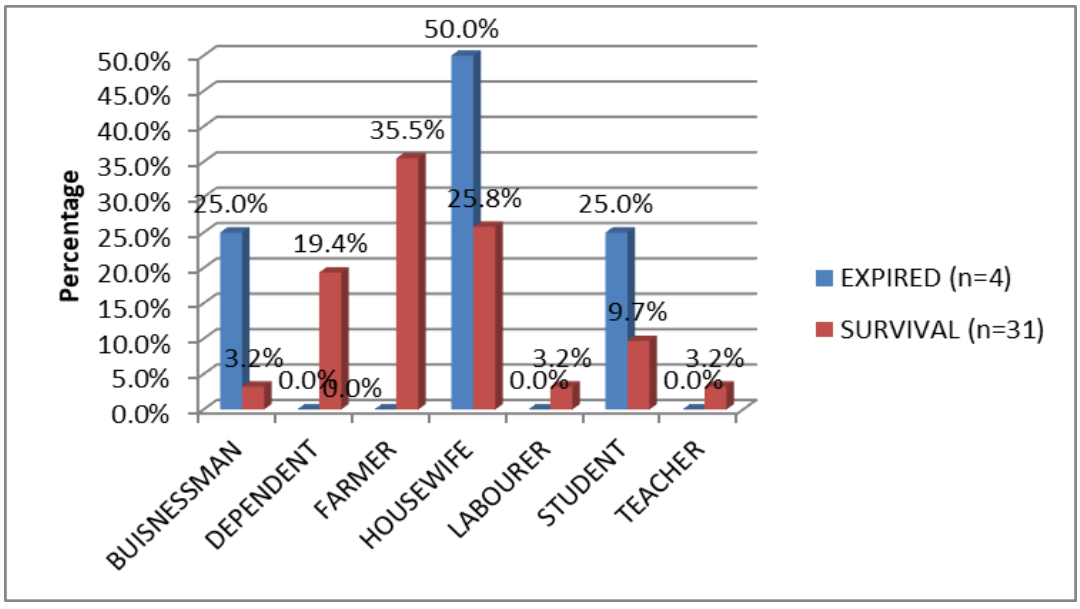
		OUTCOME				Total
		Expired (n=4)	Expired (n=4)	Survival (n=31)	Survival (n=31)	
Occupation	Buisnessman	1	25.0%	1	3.2%	2
	Dependent	0	0.0%	6	19.4%	6
	Farmer	0	0.0%	11	35.5%	11
	Housewife	2	50.0%	8	25.8%	10
	Labourer	0	0.0%	1	3.2%	1
	Student	1	25.0%	3	9.7%	4
	Teacher	0	0.0%	1	3.2%	1

n=total number of patients %=percentage of patients

Survival rate (35.5%) was maximum among farmers in our study

FIGURE- XXXXXIX

OCCUPATION



Survival rate (35.5%) was maximum among farmers in our study

TABLE- XXXXXIX

CO-MORBID CONDITIONS

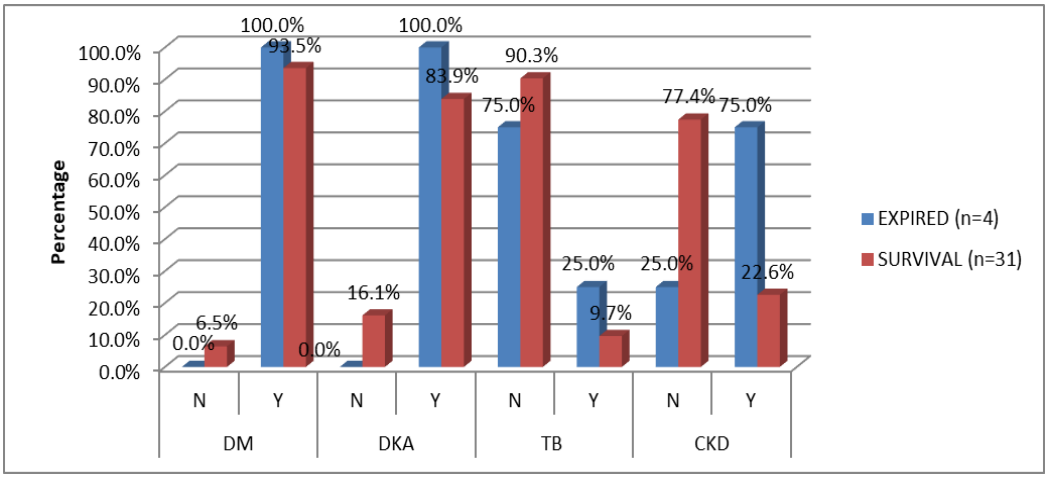
		Outcome				Total	Chi-square value	p-value
		Expired (n=4)		Survival (n=31)				
Diabetes mellitus	N	0	0.0%	2	6.5%	2	0.274	0.601
	Y	4	100.0%	29	93.5%	33		
Diabetic ketoacidosis	N	0	0.0%	5	16.1%	5	0.753	0.386
	Y	4	100.0%	26	83.9%	30		
Tuberculosis	N	3	75.0%	28	90.3%	31	0.822	0.365
	Y	1	25.0%	3	9.7%	4		
Chronic kidney disease	N	1	25.0%	24	77.4%	25	4.77	0.061
	Y	3	75.0%	7	22.6%	10		

n=total number of patients %=percentage of patients

All the expired patients were in diabetic ketoacidosis while 3 had chronic kidney disease and one had tuberculosis. Among survivor diabetic ketoacidosis was present in 83.9 % of the patients in our study (p-value-0.386)

FIGURE- XXXXXX

UNDERLYING CONDITIONS



All the expired patients were in diabetic ketoacidosis while 3 had chronic kidney disease and one had tuberculosis. Among survivor diabetic ketoacidosis was present in 83.9 % of the patients in our study.

TABLE- XXXXXX

PATIENT PRESENTATIONS

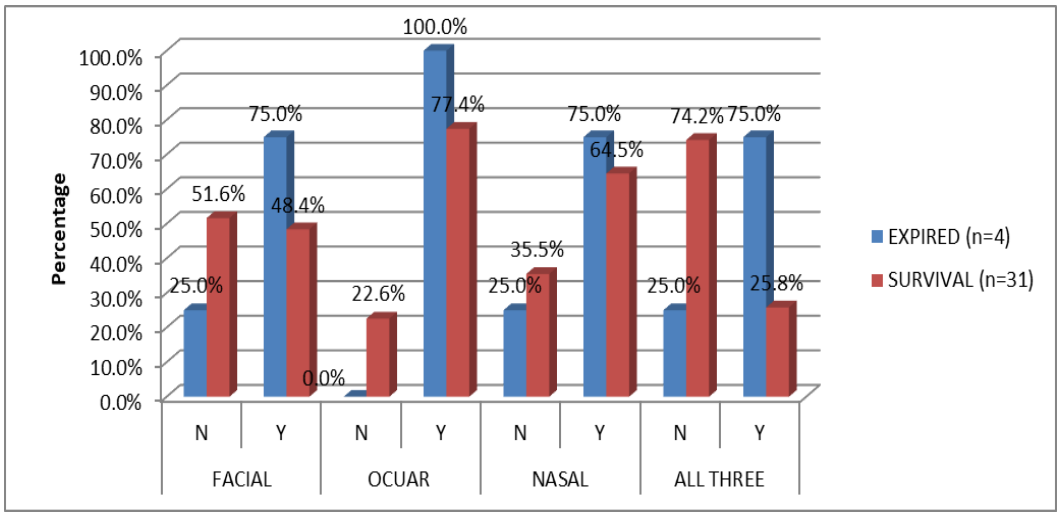
		OUTCOME				Total	Chi-square value	p-value
		EXPIRED (n=4)		SURVIVAL (n=31)				
Facial	N	1	25.0%	16	51.6%	17	1.005	0.603
	Y	3	75.0%	15	48.4%	18		
Ocular	N	0	0.0%	7	22.6%	7	1.129	0.562
	Y	4	100.0%	24	77.4%	28		
Nasal	N	1	25.0%	11	35.5%	12	0.173	0.678
	Y	3	75.0%	20	64.5%	23		
All three	N	1	25.0%	23	74.2%	24	3.978	0.082
	Y	3	75.0%	8	25.8%	11		
Total		4	100.0%	31	100.0%	35		

n=total number of patients %=percentage of patients

Patients with advanced stage of disease with nasal, facial and ocular involvement had 25.8% survival rate at 6 months in our study. p value-0.082

FIGURE- XXXXXXI

PATIENT PRESENTATIONS



Patients with advanced stage of disease with nasal, facial and ocular involvement had 25.8% survival rate at 6 months in our study.

TABLE-XXXXXXI

OUTCOME ASSOCIATION

		OUTCOME				Total	Chi-square value	p-value
		EXPIRED (n=4)		SURVIVAL (n=31)				
Age group	21-30	0	0.0%	5	16.1%	5	4.402	0.354
	31-40	2	50.0%	4	12.9%	6		
	41-50	1	25.0%	8	25.8%	9		
	51-60	1	25.0%	7	22.6%	8		
	61-75	0	0.0%	7	22.6%	7		
Sex	F	2	50.0%	8	25.8%	10	1.016	0.313
	M	2	50.0%	23	74.2%	25		
Occupation	BUISNESSMAN	1	25.0%	1	3.2%	2	6.845	0.335
	DEPENDENT	0	0.0%	6	19.4%	6		
	FARMER	0	0.0%	11	35.5%	11		
	HOUSEWIFE	2	50.0%	8	25.8%	10		
	LABOURER	0	0.0%	1	3.2%	1		
	STUDENT	1	25.0%	3	9.7%	4		
	TEACHER	0	0.0%	1	3.2%	1		
DM	N	0	0.0%	2	6.5%	2	0.274	0.601
	Y	4	100.0%	29	93.5%	33		
DKA	N	0	0.0%	5	16.1%	5	0.753	0.386
	Y	4	100.0%	26	83.9%	30		
TB	N	3	75.0%	28	90.3%	31	0.822	0.365
	Y	1	25.0%	3	9.7%	4		
CKD	N	1	25.0%	24	77.4%	25	4.77	0.061
	Y	3	75.0%	7	22.6%	10		
FACIAL	N	1	25.0%	16	51.6%	17	1.005	0.603
	Y	3	75.0%	15	48.4%	18		
OCULAR	N	0	0.0%	7	22.6%	7	1.129	0.562
	Y	4	100.0%	24	77.4%	28		
NASAL	N	1	25.0%	11	35.5%	12	0.173	0.678
	Y	3	75.0%	20	64.5%	23		
ALL THREE	N	1	25.0%	23	74.2%	24	3.978	0.082
	Y	3	75.0%	8	25.8%	11		

Patients with advanced stage of disease with nasal, facial and ocular involvement had 25.8% survival rate at 6 months in our study.

All the expired patients were in diabetic ketoacidosis while 3 had chronic kidney disease and one had tuberculosis. Among survivor diabetic ketoacidosis was present in 83.9 % of the patients in our study.

DISCUSSION

Mucormycosis, earlier an uncommon entity is now a debilitating invasive fungal infection in the developing countries with an aggressive behaviour and a fatal outcome. The department of otorhinolaryngology and Head & Neck surgery in collaboration with medicine,pathology and microbiology services of Dayanand medical college & Hospital Ludhiana undertook a study on mucormycosis patients in the period of one year i.e January to December 2018. Our prospective study analysed, 40 subjects admitted with clinical and tissue diagnosis of sino nasal mucormycosis.Medical and surgical interventions were carried out as the case may be.The patients were followed up for a period of one year with minimum follow up of 6 months.

A) DEMOGRAPHIC PROFILE

In our study maximum patients were in the age group of 41-50 yrs (27.5 %) with the mean age of 46.4 years. Youngest patient was 23 years and eldest 76 years.Male patients 30 (75%) outnumbered the females (25%).

Bhansali et al [156] 2004 study on 35 patients, reported age range as 18 to 70 years with a mean age of 47.3 (SD±14.4) with 65 % male patients.

Roden et al 2005[5] study on 900 subjects reported the mean age of patients as 38.8 years; with 65% male subjects.

Vaughan et al 2018[160] meta analysis of 175 subjects, detected 68.5% patients to be male.

In our study 92.5% of patients were residents of the state of Punjab and out of which most were residents (35%) of central Punjab comprising of Ludhiana and Moga. Majority of patients were from rural background and farmer by occupation (32.5%).

Bala et al [80] 2015 conducted a study on 38 patients in northern India which showed most patients were residents of the state of Haryana (43.6%), followed by Punjab (41.1%)

This study was conducted at a tertiary referral centre with patient drainage from the entire northern India i.e Jammu & Kashmir,Punjab, Haryana,Himachal Pradesh .

B) CLINICAL PROFILE

In the present DMCH study 72.5% of the patients had ocular presentation followed by nasal (65%). Only 12 patients (30%) presented with advanced disease with nasal, ocular and facial manifestation.

Periorbital swelling (70%), vision loss (67.5%) and rhinnorhea (62.5%) were the prominent complaints.

52.5% of patients had nasal crusting with involvement of left side nasal cavity in 66.7. 47.5 % patients had facial hypoesthesia and facial swelling was in 45 %.

Bhansali et al 2004 [156] concluded from their study of 35 patients that, ophthalmic symptoms i.e external ophthalmoplegia (89%), proptosis (83%), visual loss (80%), chemosis (74%) were more pronounced

Hernández OP et al 2015 [154] retrospective, longitudinal analysis of 11 patients, reported nasal crusting (80%), facial hypoesthesia (60%) and facial paralysis (40%).

100% of the patients had ophthalmological issues.

Yohai et al [150]1994 study of 145 cases found facial swelling (30%), facial parasthesias (20%), nasal mucosa necrosis in 48% of their patients

In our study on 40 patients frequency of ocular symptoms (70%) is similar to Yohai et al 1994[150] study on 145 patients who reported 64-67% of patients having ocular symptoms.

In our study, Patients with ocular symptoms reported within 1 week of onset of symptoms, whilst patients who had facial involvement reported with a longer disease interval of 2 weeks. Shorter duration of symptoms and early presentation reflects on the acute fulminant nature of the disease.

Left sided nasal cavity (66.7%) was predominantly involved in our study. There has been no previous study conducted to state site predominance .inferior and middle turbinate were involved more on left

side with these patients having septal deviation towards right. This indicates spores are lodged in the more roomy nasal cavity .

Palatal necrosis and skin eschar was present in 22.5% of the patients in our 40 patient study. Ferry et al 1983[155] study of 16 subjects reported eschar formation on skin or palate in only 19% of their patients. Yohai et al 1994[150] study of 145 patients reported palatal necrosis in 32% of their patients of rhino-orbital mucormycosis.

80% of patients had history of headache and 72.5% of the patients had fever in our study. Lemarroy et al 2014[222] study on 14 patients, reported fever (71.4%) as the common presenting complaint in 71.4 percent patients.Vaughan C et al[160] 2018 metaanalysis of 175 patients observed fever (26–44%), headache (5–25%) as the common associated symptoms.

C) CO-MORBID CONDITIONS

Common risk factors associated with sinonasal mucormycosis include diabetes mellitus, especially ketoacidosis, chronic kidney disease, Immunosuppressive states like haematologic malignancies, post organ transplant, chronic steroid use and neutropenia.

95% patients in our study were diabetics, out of which 92.1% presented with ketoacidosis, followed by chronic kidney disease in 27.5%.

High frequency of diabetes may be explained by the fact that in a developing country like India, many diabetics are unaware of their condition hence leading to uncontrolled hyperglycemia and ketoacidosis. This predisposes the patients to this devastating infection.

Nithyanandam et al 2003[77] study on 34 patients, reported Uncontrolled diabetes in 30 (88.2%) patients as the commonest underlying disease and 16 (53.3%) of 30 diabetics had ketoacidosis. Chronic renal failure, hepatic disease and idiopathic thrombocytopenia were the other underlying diseases reported by them.

Soumya ms et al 2014[205] study of 60 subjects ,the most common underlying condition was diabetes mellitus in 71.6% of the patients and Chronic renal failure with diabetes mellitus was underlying cause for mucormycosis in 5 patients.

Ferry et al 1983[155] study reported 16 cases of Rhino orbito cerebral mucormycosis with 13 (81%) of them having diabetes and Yohai et al 1994 reviewed 145 case reports , 60% of them had diabetes.

Diwakar *et al*. 2007[48] study of 179 subjects of paranasal sinus mucormycosis reported 70% of patients with underlying diabetic ketoacidosis.

Chakrabarti *et al.* 2009[46] study reported that nearly 50% patients had uncontrolled diabetes mellitus.

Roden et al 2005[5] study had 337 paranasal sinus mucormycosis patients with diabetes in 66% of patients

Anaemia was the most common laboratory parameter affected in our study, 92.5% of the patients. No study has previously been conducted to study this parameter.

Elinav et al study 2009 of 929 cases revealed[52] that 9.06% of all mucormycosis patients had no predisposing conditions. While in our study only 5% of the patients had no underlying comorbid condition.

D) ENDOSCOPIC PROFILE

The infection usually starts from the nose and paranasal sinuses, where it causes nasal discharge and nasal blockade, and progressive formation of necrotic eschar on the mucosa of the nose, most frequently on the middle and inferior turbinate. Middle turbinate (82.5%) and inferior turbinate (82.5%) were the predominant sites involved in our study on nasal endoscopy. Both Inferior and middle turbinate were involved in 70% of our patients

Nithyanandam et al 2003[77] study of 34 patients, reported necrosis of the turbinates in 88.2% of the patients.

Gillespie et al 1998[163] study of 25 patients, out of the 25 patients who underwent nasal biopsy, 62% had middle turbinate as the common site of fungal invasion.

Yohai et al 1994[150] study of 145 patients, reported 48% patients with nasal ulceration and presence of necrotic nasal eschar.

Our study on 40 subjects matches with Nithyanandam et al study on 34 subjects.

This could be explained by the fact that being the primary nasal air filter, middle turbinate is exposed to the maximal volume of airflow so there is increasing likelihood of fungal seeding due to mucosal disruption and mucociliary damage.

E) ORBITAL INVOLVEMENT

In our study total ophthalmoplegia was present in 57.5% of the patients with central retinal artery occlusion in 50% on fundus examination. Extraocular muscle were involved in 65% of the patients and 62.5% of patients had conjunctival chemosis.

Nithyanandam et al 2003[77] study of 34 subjects reported in their retrospective analysis opthalmoplegia in 67.6%, central retinal artery occlusion in 50%, chemosis in 67.6% and proptosis in 41.2% of their patients.

F) NEUROLOGICAL PROFILE

In our study VIth cranial nerve (abducent) was the most common cranial nerve involved in 70% of the patients followed by IIIrd and IVth nerve in 65% patients.

Bhansali et al 2004[156] study reported VI nerve palsy in 46% of the patients.

Corzo-Leon et al.[157] reported cranial nerve palsy and diplopia and they proposed an algorithm for the diagnosis of rhinocerebral mucormycosis.

Kavita Sachdeva[218] 2013 reported six patients suffering from diabetes mellitus with biopsy proven mucormycosis involving 2nd, 3rd, 4th, 5th, 6th and 7th cranial nerves .

Jiang et al 2016 study[223] of 11 patients of invasive rhino-orbito-cerebral mucormycosis reported orbital apex syndrome had cranial nerve (3,4,6th) involvement in all the 11 cases.

Facial nerve was involved in 12.5% of our patients. Ferry et al.[155] 1983 study of 16 subjects reported frequency of facial nerve paralysis in conjunction with rhino-orbital-cerebral mucormycosis in 11% subjects.

G) IMAGING PROFILE

In our study Paranasal sinus opacification was present in 57.5% of our patients followed by mucosal thickening in 42.5% and bone erosion in 17.5% of the patients on imaging study. Maxillary sinus (97.5%) was predominant sinus involved followed by the ethmoid sinus (95%) in our study.

Bhansali et al study 2014[156] had all 35 patients with evidence of paranasal sinuses involvement on computed tomography/magnetic resonance imaging, The ethmoid (86%) and maxillary sinuses (80%) were commonly involved.

Jacob theraKathu et al study, 2018[141] of 43 patients, on computed tomography and magnetic resonance imaging reported predominant involvement of the ethmoid (37,86%) and maxillary (34,79%) sinuses with main finding of mucosal thickening of paranasal sinuses.

Bala et al 2011[80] study of 24 cases, noted Paranasal sinus opacification in 58.3% of the cases .they did not specify separately which sinus was the most involved.

In our study peripheral to sinus involvement was seen in 35% of the patients with Infratemporal fossa being the most common extra sinus site (64.3%) involved.

Jacob therakathu et al 2018 study[141] of 43 patients, reported 60% of the patients showing extrasinus extension across grossly intact appearing bones on imaging. Due to the angioinvasive nature of the disease, bone involvement is usually seen late in the disease.

Hosseini *et al*. 2005 study[165] on 10 patients concluded that the pterygopalatine fossa is a reservoir of the disease through which it can spread to the neighbouring structures, including the retro global space of the orbit and the infratemporal fossa.

In our study orbital involvement was observed in 80% of patients.

Orbital cellulitis was present in 77.8 % of the patients with cavernous sinus thrombosis in 11%, while proptosis in 44.4%.

H) MYCOLOGICAL PROFILE

Tissue diagnosis was made on histopathological examination and KOH preparation/fungal culture of specimens obtained from the nasal cavity and paranasal sinuses or the palate.

Mucor is not easy to isolate and maintain in a laboratory because their poorly septate hyphae can loose the vital cytoplasm at the least manipulation. Therefore, histopathological examination was carried out in all our subjects while fungal smear KOH and fungal culture was undertaken in 31 and 29 patients respectively.

All our 40 patients (100%) were diagnosed as cases of zygomycosis on histopathological examination of the excised tissue.

KOH examination showed aseptate hyphae in 61.3% (19) of the patients while septate hyphae in 38.7% of the patients.

Fungal culture isolates from the involved tissue showed growth of mucor in 5 (17.2 %) patients

Bhansali et al 2004 [156] study of 35 subjects, the diagnosis of rhino-orbito-cerebral mucormycosis was based on direct microscopy of aspirate/crusts from the nasal/sinus mucosa in 14 (40%), on histopathology in 11 (31%), and on both in 10 (29%). Culture on Sabroud's media was performed in 28 patients and was reported positive in 7(25%) patients Rhizopus spp, 1; Rhizopus rhizopodoformis, 1;Rhizopus arrhizus, 4;Mucor spp .

I) MEDICAL THERAPEUTICS

Amphotericin B deoxycholate (AmB) and its lipid derivatives remain the mainstay of medical therapeutics in mucormycosis.

All our patients were administered Amphotericin b except one who dropped treatment in between against medical advice probably due to financial constraints.

56.4% of our patients were given Liposomal amphotericin b while conventional amphotericin b was given in 43.6 % of the patients. Amphotericin b (liposomal) was given in the dose of 2-3 grams in 51.3% of the patients and 1-2 grams (conventional) in 33.3% of the patients. Regular monitoring of renal function was by serum creatinine levels. Serum creatinine values were less than 1.5 gm/dl in 60% of the

patients while it was more than 2 mg/dl in 30% of the patients. Despite treatment 4 patients expired due to underlying complications such as cardiorespiratory collapse and septic shock.

Bhansali et al 2004 [156] reported the use of amphotericin B in their 35 patients, with total doses varying from 3.0–3.5 grams.

In Nithyanandam et al 2003 study [77], thirty-three patients received intravenous amphotericin B as soon as a diagnosis of mucor was established. And the cumulative dose ranged from 25miligrams to 2500 miligrams.

J) SURGICAL THERAPEUTICS

Radical Nasal debridement was carried out in all the (100%) patients along with orbital exenteration and maxillectomy in 15% of the patients in our study.

Bala et al 2011[80] study reported surgical debridement in 18 cases of rhino-orbital mucormycosis.

Nithyanandam et al 2003[77], retrospective analysis of 34 patients had 11 patients who underwent sinonasal debridement, 7 sinonasal debridement with local amphotericin b irrigation and 9 patients underwent orbital exenteration with sinonasal debridement and partial maxillectomy and necrosed tissue was excised in 4.

Bhansali et al 2004 study [156], 26 patients were subjected to appropriate surgery including lateral rhinotomy, sinusectomy, orbital exenteration (11/26), and frontotemporal craniotomy.

Somya MS et al 2014[205] retrospectively reviewed 60 patients out of which 38 patients underwent debridement, 10 orbital exenteration and 12 received periorbital amphotericin b injection

M. Musharaf. Baig et al 2007 [204] study reported surgical interventions as sinusectomy, partial or radical maxillectomy, debridement of the cheek soft tissue and pterygopalatine fossa with or without orbital exenteration.

K) OUTCOME FACTORS

In our study survival rate at 6 month follow up was 77.5 % i.e 31 patients survived out of 40 patients and expired

Outcome was unfavourable in 4 patients who expired.

Most of the patients who survived were in the age group of 41-50 years with 74.2% of the survivors being male.

All the 4 patients who expired had diabetic ketoacidosis while 3 of them had chronic kidney disease and one had history of tuberculosis in the past. However, diabetic ketoacidosis did not significantly affect the survival outcome (p. 0.386) in our study.

Patients with advanced stage of the disease i.e., nasal, facial and ocular involvement had 25.8 % survival rate in our study at 6 months with medical and surgical intervention

Blitzer et al 1980[35] observed that the underlying disease was an important determinant of survival. They noted that 75% of patients had no systemic disease, 60% of diabetics, and 20% of patients with other haemato-oncologic disorders survived.

In Nithyanandam et al 2003[77] study of 34 patients; patients who underwent sinonasal debridement had the best outcome i.e. in 17 of 18 (94.4%) patients. Treatment failure was seen in 8 of 9 (88.9%) patients with orbital exenteration. Seven of these patients died due to uncontrolled disease and one patient was discharged on request with spread of infection to the contralateral side. All the patients treated with amphotericin b alone expired due to uncontrolled disease. Thus, treatment success was seen in 18 (52.9%) patients, treatment failure in 16 (47.1%) and the overall mortality was 32.4% (11 patients).

Bhansali et al 2004[156] retrospective study, out of 35 patients treated with both amphotericin b and surgical debridement twenty one patients survived, four left against medical advice, and 10 died; with survival rate of 60%. Duration of follow up ranged from 10 months to 11 years with a mean (SD) of 39.6 (34.1) months. However, diabetic ketoacidosis did not affect the survival outcome ($p > 0.05$) in their study of rhino-orbital-cerebral mucormycosis in patients with diabetes.

Rangel et al 1985 study [37] reported survival rate of 68% in 22 patients who underwent surgical debridement and amphotericin b administration.

Bala et al 2015[80] prospective study included 24 cases and combination of surgery and medical treatment with amphotericin b was

significantly better (OR = 0.2, *P*< 0.04) than amphotericin B alone (61.5% vs. 10.3% patient survival).

Vaughen c et al 2018[160] metanalysis of 175 cases found overall survival rate was 59.5% which was almost the same as previous series reported (60%) reported by Yohai et al study of 145 patients in 1994.

Vaughen c et al 2018[160] meta analysis reported improved survival rates in patients with chronic renal disease ie from 19% to 52% but Survival rate in our study at 6 month follow up in patients with chronic kidney disease was 22.6% (7/31patients), outcome was unfavourable in 3 patients .

The higher overall survival rate in our study may be because of early diagnoses and initiation of treatment promptly on basis of high clinical suspicion. Thus, our study emphasizes the necessity of spreading awareness about the disease and aggressive measures for early diagnosis and management.

COMPARATIVE SUMMARY

	DMCH Study (2017-18)		**World Literature**			
Parameter /Sr.No.	Subjects number	Outcome	Study group	Study year	Subjects number	outcome
DEMOGRAPHIC PROFILE						
Mean age	40	46.4yrs	Bhansali et al[156]	2004	35	47.3yrs
			Roden et al[5]	2005	337	38.8yrs
Gender ratio (male:female)	40	3:1	Vaughen et al 2018[160]	2018	175	2.1:1
			Bhansali et al[156]	2004	35	1.8:1
Geographic predominance	40	92.5%	Bala et al[80]	2011	38	41.1%
CLINICAL PROFILE						
Nasal crusting	40	52.5%	Yohai et al[150]	1994	145	80%
Rhinorrhea	40	62.5 %	Lemarroy et al[222]	2014	14	57.1%
Facial hypoesthesia	40	47.5%	Bhansali et al[156]	2004	35	34%
			Hernandez op et al[154]	2015	11	60%
Facial swelling	40	45%	Bhansali et al[156]	2004	35	46%
			Yohai et al[150]	1994	145	30%
Periorbital swelling	40	70%				
Vision loss	40	67.5%	Bhansali et al[156]	2004	35	80%
Palatal necrosis	40	22.5%	Yohai et al[150]	1994	145	32%
Skin eschar	40	22.5%	Ferry et al[27]	1983	16	19%
			Bhansali et al[156]	2004	35	11%
Fever	40	72.5%	Lemarroy et al[222]	2014	28	71.4%
Opthamloplegia	40	57.5%	Nithyanandam et al[77]	2003	34	67.6%

Proptosis	40		Nithyanandam et al[77]	2003	34	41.2%
			Bhansali et al[156]	2004	35	83%
Chemosis	40	62.5%	Nithyanandam et al[77]	2003	34	67.6%
			Bhansali et al[156]	2004	35	74%
Central retinal artery occlusion	40	50%	Nithyanandam et al[77]	2003	34	50%
Diabetes mellitus	40	95%	Nithyanandam et al[77]	2003	34	88.2%
			Roden et al[5]	2005	337	66%
			Yohai et al[150]	1994	145	60%
			Chakrabarti et al[47]	2009		50%
			Diwarkar et al[48]	2007	179	70%
Chronic kidney disease	40	27.5%	Nithyanandam et al[77]	2003	34	10%
Anemia	40	92.5%	No data available			
Alcohol addiction	40	72.5%	No data available			
No underlying condition	40	5%	Elinav et al[52]	2009	929	9.06%
ENDOSCOPIC PROFILE						
Involvement of middle and inferior turbinate	40	82.5%	Yohai et al[150]	1994	145	48%
			Nithyanandam et al[77]	2003	34	88.2%
IMAGING STUDYPROFILE						
Paranasal sinus opacification	40	57.5%	Bala et al[80]	2011	24	58.3%
Paranasal sinus mucosal thickening	40	42.5%	Jacob therakatu et al[141]	2018	43	100%
Bone erosion	40	17.5%	Jacob	2018	43	40%

			therakatu et al[141]			
Maxillary sinus involvement	40	97.5%	Bhansali et al[156]	2014	35	80%
Ethmoid sinus involvemnt	40	95%	Bhansali et al[156]	2014	35	86%
Extra sinus involvement	40	35%	Jacob therakathu et al[141]	2018	43	60%
Orbit involvement	40	45%	Jacob therakatu et al[141]	2018	43	60%
Cavernous sinus thrombosi	40	11%	Jacob therakatu et al[141]	2018	43	14%
			Bhansali et al[156]	2014	35	11%
NEUROLOGICAL PROFILE						
6th nerve involvement	40	70%	Bhansali et al[156]	2014	35	46%
			Nithyanandam et al[77]	2003	34	29.4%
7th nerve involvement	40	12.5%	Ferry et al[27]			11%
			Nithyanandam et al[77]	2003	34	32.4%
MYCOLOGICAL PROFILE						
Koh positivity	40	61.3%	Bala et al[80]	2011	24	40%
Fungal culture-mucor	40	17.2%	Bala et al[80]	2011	24	25%
Histopathological zygomycetes	40	100%	Bala et al[80]	2011	24	31%
MEDICALTHERAPEUTICS						
amphotericin b Administration	40	97.5%	Bhansali et al[156]	2014	35	100%
			Nithyanandam et al[77]	2003	34	97%
Dose range of amphotericin	40	850mg-	Bhansali et	2014	35	3-3.5gm

b given		3000mg	al[156]			
			Nithyanandam et al[77]	2003	34	25-2500mg
SURGICALTHERAPEUTICS						
Nasal debridement	40	100%	Somya MS et al[205]	2014	60	63.3%
			Bala et al[80]	2011	24	70.8%
			Nithyanandam et al[77]	2003	34	50%
			Bhansali et al[156]	2014	35	74.2%
Orbital exenteration	40	15%	Somya MS et al[205]	2014	60	16%
			Nithyanandam et al[77]	2003	34	26.4%
Maxillectomy	40	15%	Nithyanandam et al[77]	2003	34	26.4%
SURVIVAL RATE						
	40	77.5%	Bhansali et al[156]	2014	35	60%
			Nithyanandam et al[77]	2003	34	67.6%
			Bala et al[80]	2011	24	83%
			Rangel et al[37]	1985	22	68%

SUMMARY & CONCLUSION

The present study on Rhino sino orbital mucormycosis on 40 subjects, was undertaken at a tertiary health care facility of north India, in the state of Punjab, at the department of otorhinolaryngology and head &neck surgery.The study was in collaboration with medicine, microbiology and pathology services of Dayanand Medical College & Hospital Ludhiana. The study period was January to December 2018.

The characteristics features regarding rhino sino orbital mucormycosis concluded from the present study are:

- Age group-41-50 years was predominant
- Gender – Male: female ratio-3:1
- Comorbidity -Diabetes (95%) followed by chronic kidney disease (27.5%)
- Presentation -Ocular followed by nasal
- Middle turbinate and inferior turbinate were commonly involved sites (70%), as visualized on nasal endoscopy.
- Anaemia was also a predominant risk factor, being present in 92.5% of the patients which has not been reported till date in the world literature.
- Left sided nasal cavity (66.7%) was predominantly involved in our study while deviated nasal septum towards right side was noted, which has not been reported till date in the world literature.
- Computed tomography scans showed equal involvement of maxillary (97.5%) and ethmoid sinuses (95%).
- Sixth nerve palsy was the predominant involvement (70%) seen in our study.
- Outcome-Overall survival rate with Medical and surgical intervention at 6 month follow up was 77.5%
- Debridement was performed in our patients which facilitated a favourable outcome.
- Predominant age group among survivors -41-50 years

- 74.2 % of the survivors were male in our study.
- Survival rate in Diabetes mellitus- 83.9%
- Survival rate in Chronic kidney disease- 22.6%
- Survival rate with Ocular+ facial+ nasal presentation- 25.8%

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CLINICAL PRESENTATION

(comparison with either side)

- OCULAR

Case-i Conjunctival chemosis (left)

Case-ii Periorbital edema (right)

Case-iii Fixed dilated pupil with frozen globe (left)

Case-iv Ptosis (left)

Case-v Periorbital swelling (right)

Faces and eyes are not covered for comparison with the normal side

- FACIAL

Case-i Necrotic crusting over hard palate

Case-ii Whitish debris with bone erosion

Case-iii Palatal necrosis

Case-iv Palatal ulcer

Case-v Palatal eschar

Case-vi Ischaemic changes

Faces and eyes are not covered for comparison with the normal side

- **SKIN ESCHAR**

Case-i Eyelid eschar

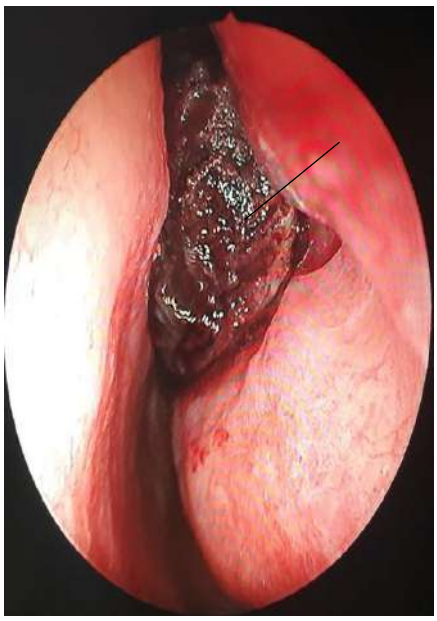
Case-ii Alar eschar

Case-iii Eschar right face

Case-iv Alar skin and upper lip

Faces and eyes are not covered for comparison with the normal side

ENDOSCOPIC PROFILE -



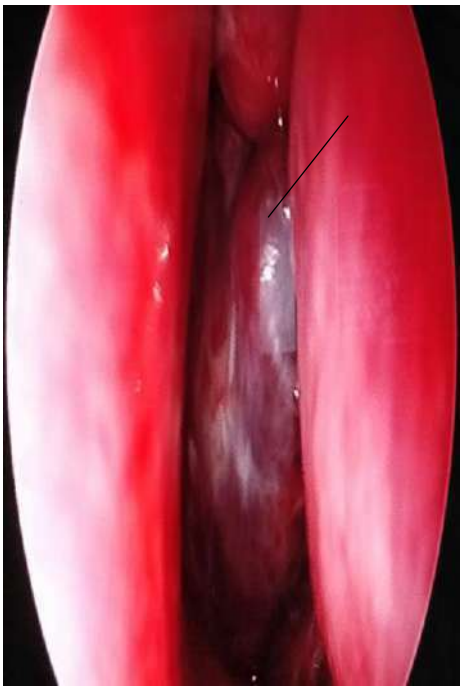
Case –i Necrotic middle turbinate (left)

Case-ii Ischaemic posterior end middle turbinate (right)

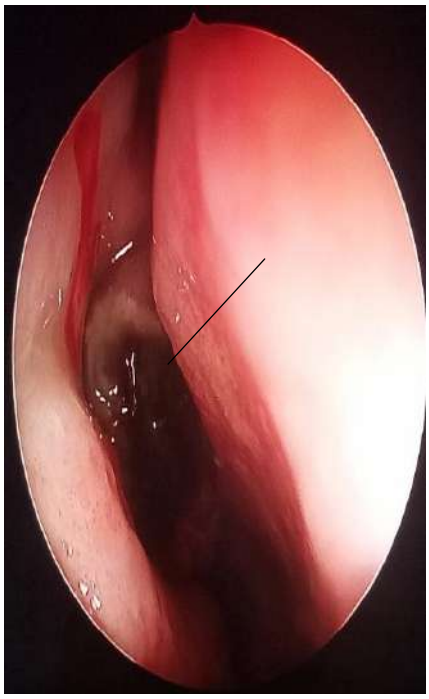
Case-iii Necrotic crusting over inferior turbinate(left) &septum(left)

Case-iv Ischaemic middle turbinate (left)

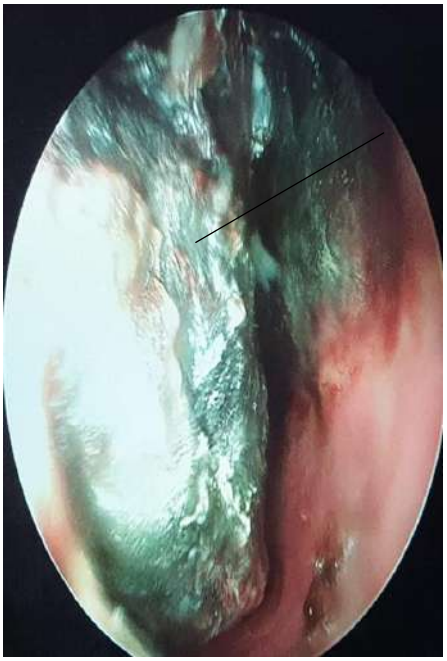
Faces and eyes are not covered for comparison with the normal side



Case-iv Inflammed middle turbinate (left)



Case-v Discolouration of middle turbinate(right)

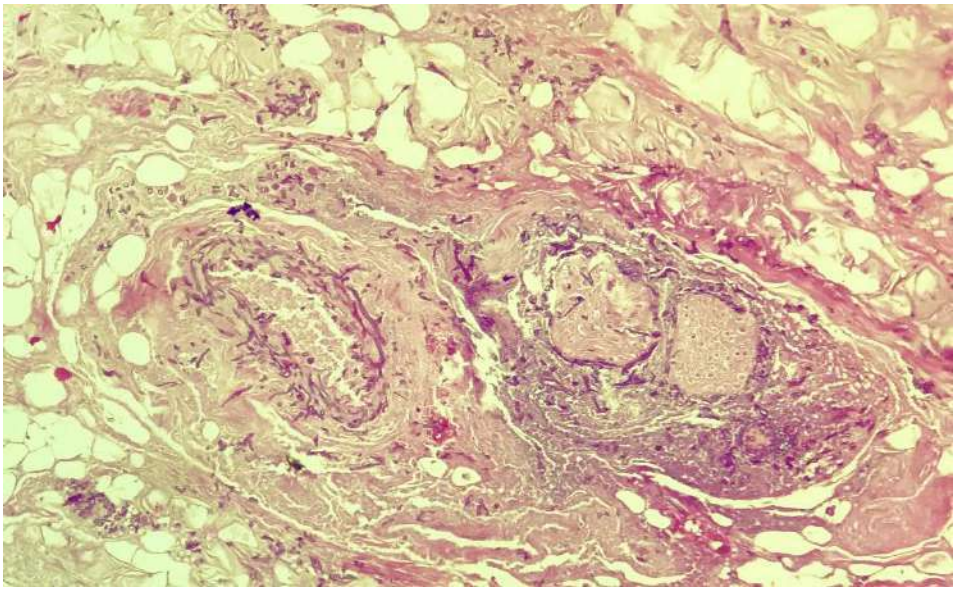


Case-vi Necrotic inferior turbinate & septum (right)

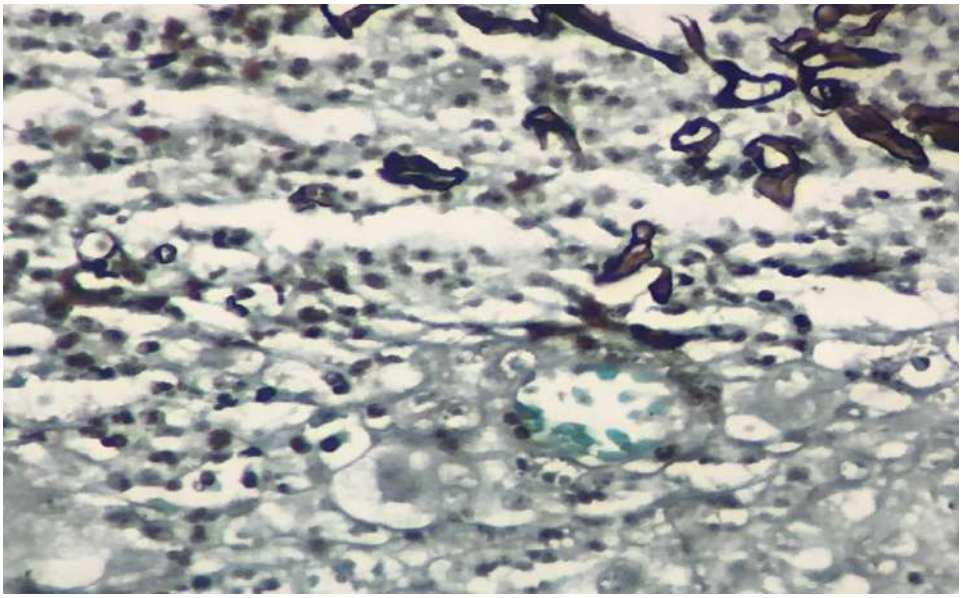
Case-vii Purulent discharge in middle meatus (left)

Faces and eyes are not covered for comparison with the normal side

MYCOLOGICAL PROFILE



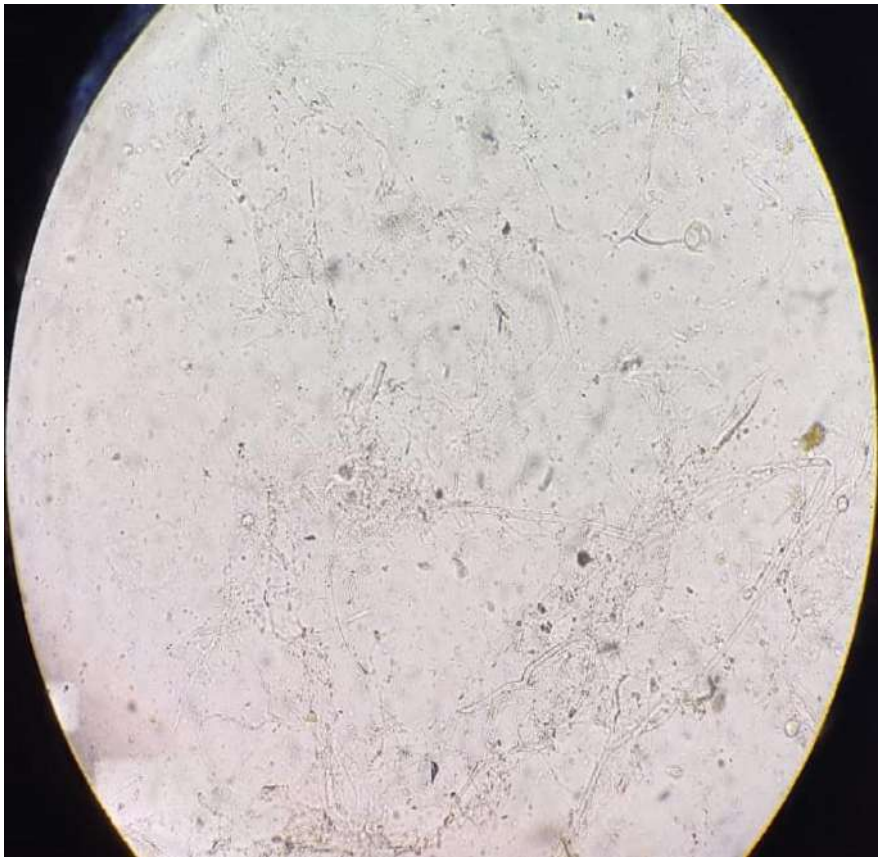
Photomicrograph showing aseptate hyphae of Zygomycetes showing extensive vascular and perineurial invasion (PAS, X40)



Photomicrograph showing broad, aseptate hyphae of Zygomycetes (GMS, X40)

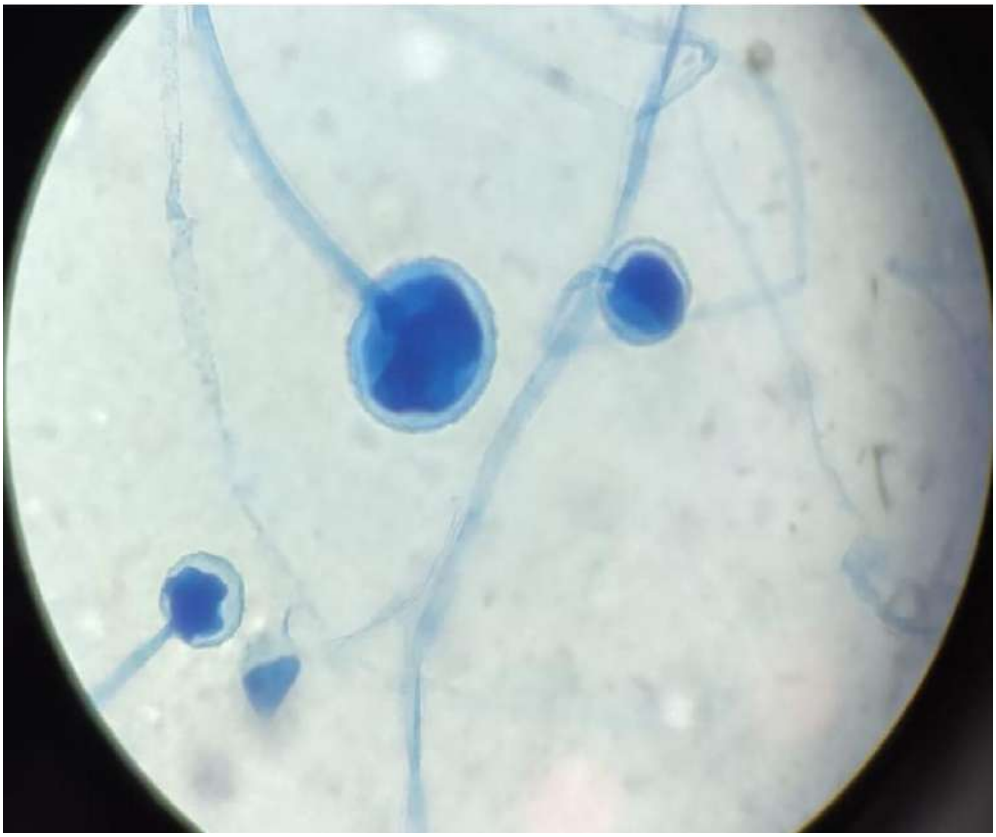
Faces and eyes are not covered for comparison with the normal side

KOH MOUNT showing hyaline aseptate broad ribbon shaped hyphae [400x]



KOH MOUNT showing hyaline aseptate broad ribbon shaped hyphae [100x]

Faces and eyes are not covered for comparison with the normal side

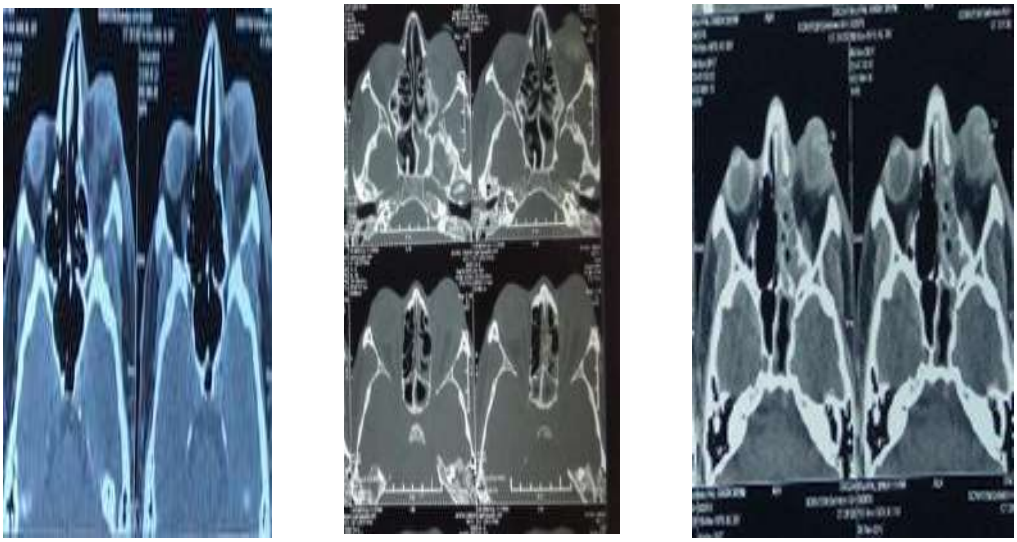


LCB MOUNT broad aseptate hyphae without rhizoids,globose sporangium containing sporangiospores[400x]

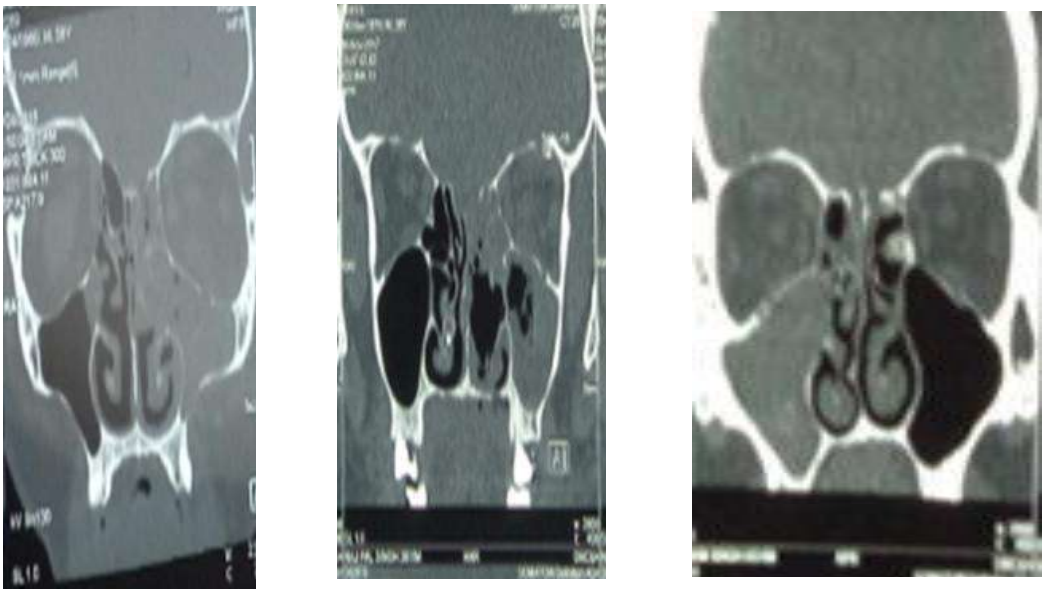
Sabauraud dextrose agar slant showing grey white colonies of mucor with a thick cottony , fluffy surface

Faces and eyes are not covered for comparison with the normal side

RADIOLOGICAL PROFILE



Axial cuts showing marked left proptosis



Coronal sections showing maxillary and ethmoid sinus opacification

Faces and eyes are not covered for comparison with the normal side

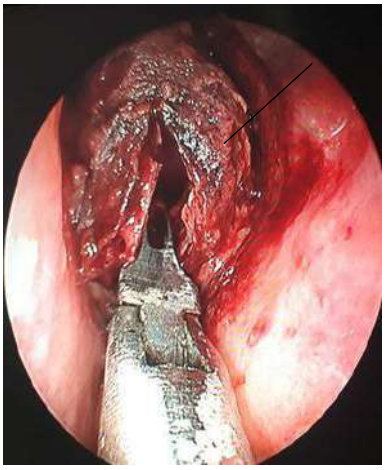
Left maxillary sinusitis with palatal erosion and erosion of lateral wall of maxillary sinus.

Coronal sections with mucosal hypertrophy of maxillary sinuses bilateral .

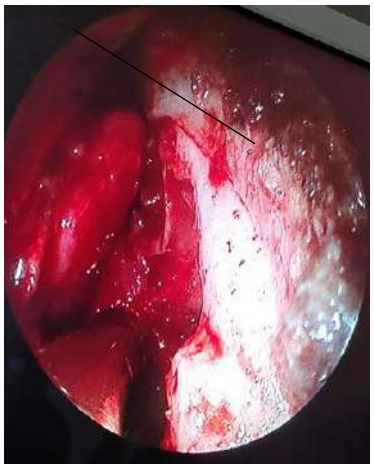
Faces and eyes are not covered for comparison with the normal side

SURGICAL THERAPEUTICS

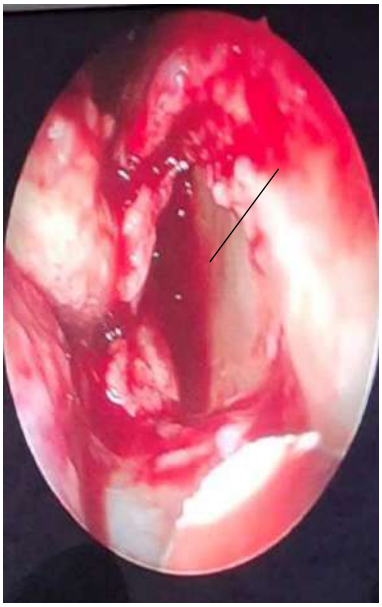
- Endoscopic nasal debridement



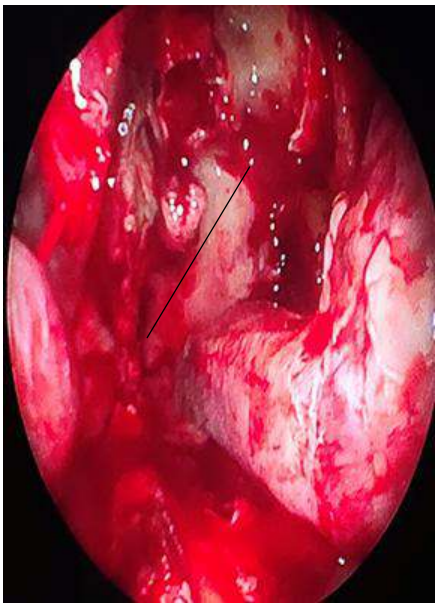
Case-i Debridement of necrotic middle turbinate left



Case-ii lateral nasal wall debridement left

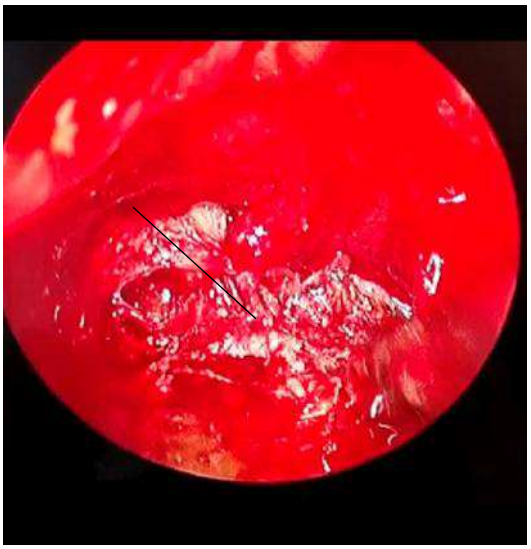


Case-iii Posterior septectomy view

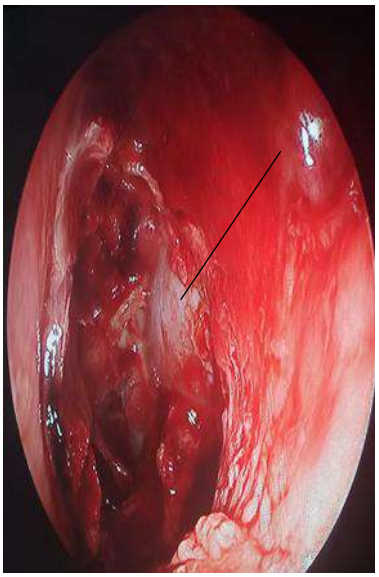


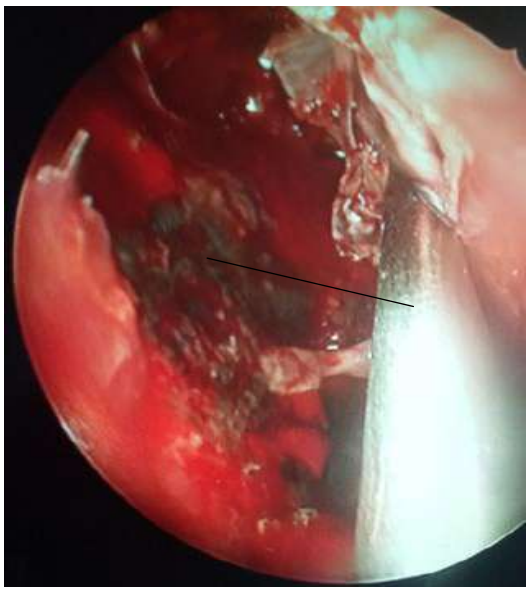
Case-iv post posterior septectomy from rightside

Faces and eyes are not covered for comparison with the normal side

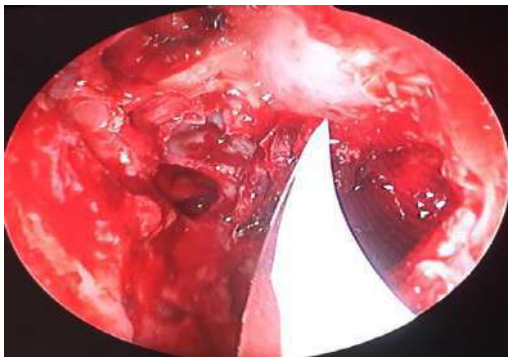


Case-v Removal of necrotic mucosa from maxillary sinus(right)and floor of sphenoid sinus





Case-vi Post middle turbinectomy ethmoid sinus clearence and shenoidotomy from right side



Case-vii post sphenoid wall clearence

Faces and eyes are not covered for comparison with the normal side

- MAXILLECTOMY

Case-i

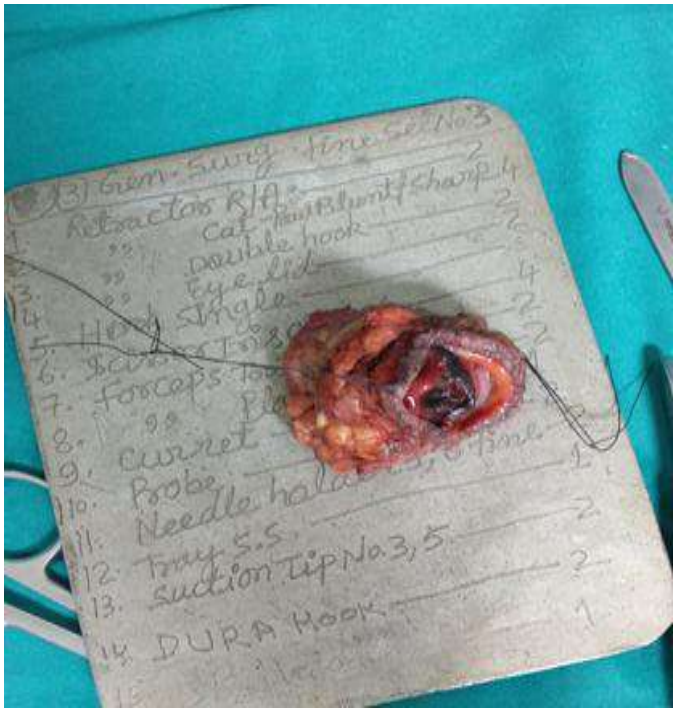
Case-ii

Faces and eyes are not covered for comparison with the normal side

- **ORBITAL EXENTERATION**

Case-I

Case-II



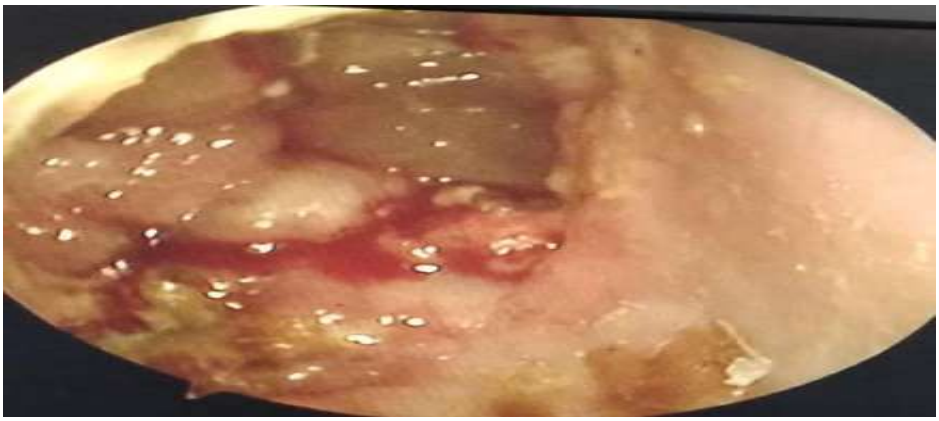
Specimen

Faces and eyes are not covered for comparison with the normal side

POST OP STATUS (1 month) ENDOSCOPIC PICS

Case-i Left sphenoethmoidal recess healthy lining

Case-ii Right healthy lining on maxillary sinus ostium



Case-iii Left crusting inferior border of widened maxillary sinus ostium and bare bone vertical plate of palatine bone

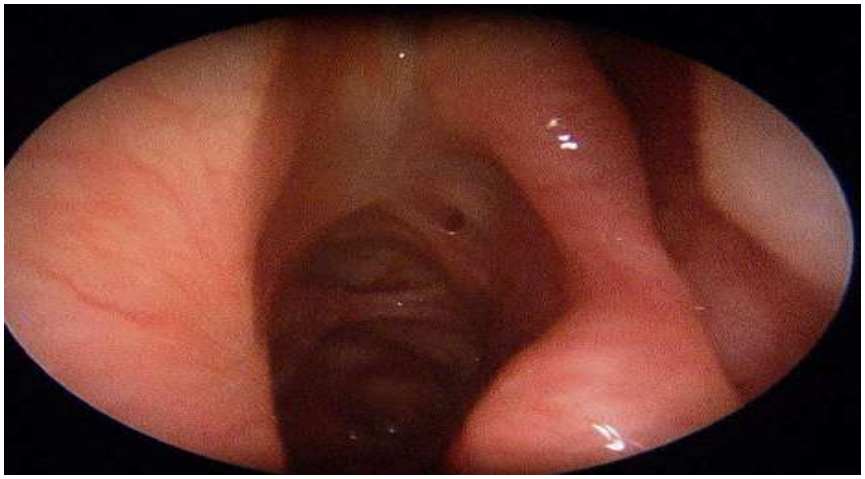
Case-iv Right oedema pad at haler cell region

Case-v Right osteomeatal complex

Faces and eyes are not covered for comparison with the normal side

Case-vi Healthy mucosa on maxillary, ethmoid sinus and ground lamella (right)

Case-vii Healthy mucosa on fovea, frontal recess (right)



Case-viii Right axilla, head of middle turbinate and frontal recess healthy mucosa

Case-ix Ethmoidal labyrinth with resected head of middle turbinate left side

Faces and eyes are not covered for comparison with the normal side

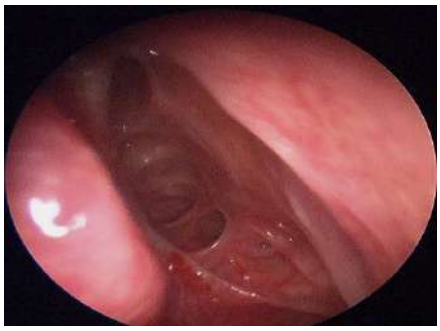
Case-x Left fovea ethmoidalis

Case-xi Edematous middle turbinate and ethmoidal region right side

Faces and eyes are not covered for comparison with the normal side

POST OP STATUS (3RD MONTH) ENDOSCOPIC PICS

Case-i Left osteomeatal unit with healthy mucosa



Case-ii Left Middle turbinate head, fovea ethmoidalis

Case-iii Healthy lining middle meatus

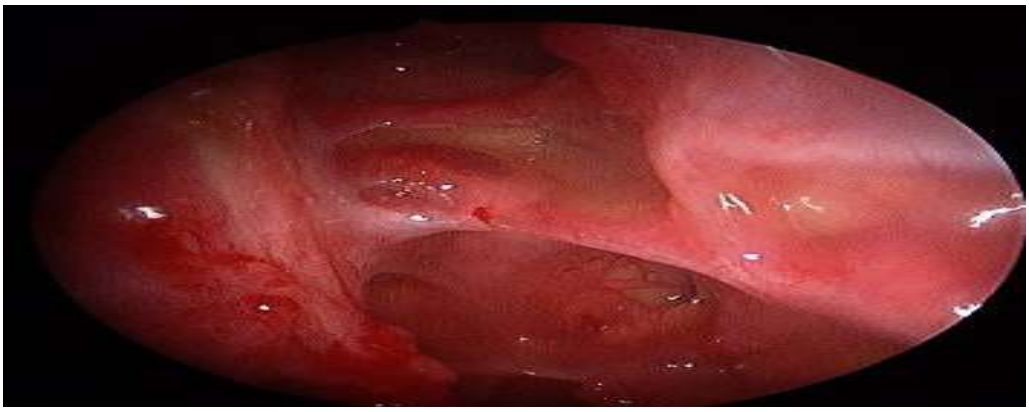
Case-iv Self cleaning right maxillary sinus ostium

Case-v Resected stump of middle turbinate and sphenoid ostium

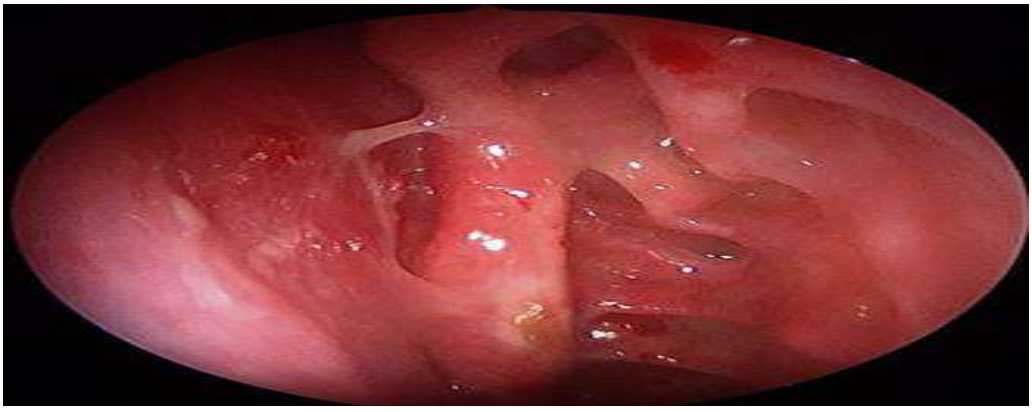
Faces and eyes are not covered for comparison with the normal side

Case-vi Left crusting head of middle turbinate

Case-vii Right Middle meatus healthy lining

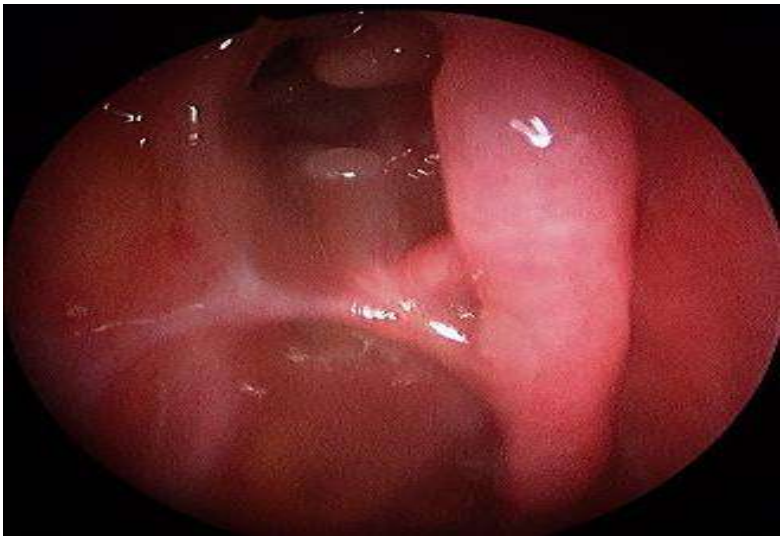


Case-viii Left frontal recess, fovea and maxillary sinus

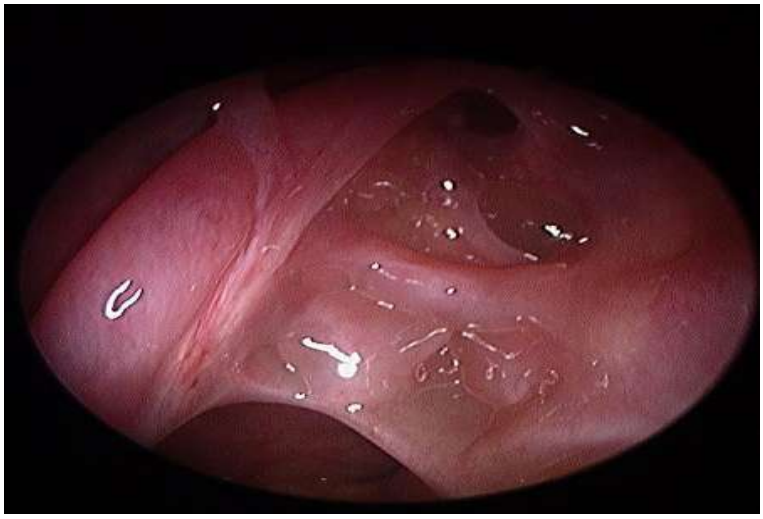


Case-ix Left healthy lining over fovea ethmoidalis, frontal recess and synechiae between middle turbinate and septum

Faces and eyes are not covered for comparison with the normal side



Case-x Right healthy lining on frontal recess



Case-xi Left scar tissue in ethmoidal labyrinth

Faces and eyes are not covered for comparison with the normal side

- POST MAXILLECTOMY -

Case-i Palatal defect right side following inferior partial maxillectomy

Case-i Healthy margins of defect ,with exposed bone at 2-4 clock maxillary sinus mucosa healthy

Faces and eyes are not covered for comparison with the normal side

Case-ii Left sided healthy lining of palatal defect

Case-ii Enlarged view showing inferior turbinate and middle meatus

Faces and eyes are not covered for comparison with the normal side

POST RADICAL DEBRIDEMENT REHABILITATION FOR FEEDING

Obturator prosthesis to fit into palatal defect

Faces and eyes are not covered for comparison with the normal side

6 MONTH FOLLOW UP (comparison of orbital region of either side)

Case-i Eyelid covering orbital rim

Case-ii Edematous upper eyelid persisting

Case-iii Dry crust noted on lower eyelashes

Case-iv Crusting on eyelashes and region of lacrimal sac

Faces and eyes are not covered for comparison with the normal side

Facial asymmetry post maxillectomy without prosthesis

Case-i

Case-ii

Faces and eyes are not covered for comparison with the normal side

							NASAL PRESENTATION				FACIAL PRESEN	
SR NO	Name	mrd no	age	sex	city	ocupation	CRUST	RHINORRHEA	OBSTRUCTION	DURATION (DAYS)	HYPOESTHESIA	SWELLING
1	R	277663	42	M	FEROZPUR	FARMER	N	N	Y(R)	60	Y(R)	Y
2	RB	286001	38	F	MOGA	HOUSEWIFE	N	N	N	-	Y(R)	Y
3	KK	303036	55	F	JLD	HOUSEWIFE	Y(R)	Y	Y(R)	30	N	N
4	HS	354287	60	M	LDH	DEPENDENT	N	N	N	-	N	N
5	VS	374362	73	M	MOGA	DEPENDENT	N	N	N	-	N	N
6	AS	382652	43	M	LDH	FARMER	Y(R)	Y	N	7	N	N
7	RS	382678	38	M	FEROZPUR	LABOURER	N	Y	Y (L)	15	N	N
8	SS	383128	45	M	MOGA	FARMER	Y (L)	Y	Y (L)	7	N	N
9	AK	389632	55	M	MOGA	DEPENDENT	N	Y	Y (L)	90	N	N
10	S	398312	65	M	LDH	DEPENDENT	N	Y	Y(R)	30	N	N
11	S	394127	61	M	BHATHINDA	FARMER	N	N	N	-	N	N
12	NK	398224	36	F	LDH	HOUSEWIFE	Y (L)	Y	Y (L)	30	Y (L)	Y
13	SS	418216	45	M	BHATHINDA	FARMER	Y (L)	Y	Y (L)	30	N	N
14	PK	423000	60	F	HOSHIARPUR	HOUSEWIFE	Y (L)	Y	Y (L)	30	N	N
15	MS	425807	64	M	PATHANKOT	DEPENDENT	Y (L)	Y	Y (L)	30	N	N
16	MB	427718	45	F	J.K	HOUSEWIFE	N	Y	N	5	N	N
17	DS	429115	23	M	MUKTSAR	STUDENT	Y (L)	Y	Y (L)	365	Y (L)	N
18	PK	454441	52	F	LDH	HOUSEWIFE	N	N	N	-	Y (L)	N
19	Z	470575	40	F	J.K	HOUSEWIFE	Y (L)	Y	Y (L)	10	Y (L)	Y
20	DS	480072	23	M	FEROZPUR	FARMER	Y(R)	Y	Y(R)	30	Y(R)	Y
21	SP	480915	44	M	JLD	FARMER	N	N	N	-	N	N
22	HS	499988	25	M	LDH	STUDENT	N	N	N	-	N	N
23	BS	509830	45	M	MUKSTAR	FARMER	Y(R)	Y	Y(R)	12	Y(R)	Y
24	KS	520072	42	M	MALERKOTLA	BUISNESSMAN	Y (L)	Y	Y (L)	30	Y (L)	Y
25	SS	572372	62	M	LDH	DEPENDENT	N	N	N	-	N	N
26	SR	582311	42	M	LDH	FARMER	N	N	N	-	Y (L)	Y
27	HS	590598	40	M	BATHINDA	FARMER	N	N	N	-	N	N
28	HS	592952	30	M	BARNALA	BUISNESSMAN	N	N	N	-	N	Y
29	DK	595181	30	M	SRS NAGAR	TEACHER	Y (L)	Y	Y (L)	30	Y (L)	Y
30	PJ	603251	58	M	J.K	TEACHER	N	N	N	-	Y (L)	Y
31	P	601609	50	M	LDH	FARMER	N	N	N	-	N	N
32	TS	607346	55	M	SANGRUR	FARMER	Y (L)	Y	Y (L)	30	Y (L)	Y
33	NK	611699	65	F	FATEHGARH	HOUSEWIFE	Y (L)	Y	Y (L)	30	Y (L)	Y
34	P	623320	23	M	FAZILKA	STUDENT	Y (L)	Y	Y (L)	10	Y (L)	Y
35	MA	631012	34	M	MALERKOTLA	BUISNESSMAN	Y(R)	Y	Y(R)	30	Y(R)	Y
36	R	647290	32	M	FEROZPUR	STUDENT	Y(R)	Y	Y(R)	3	Y(R)	Y
37	JK	656160	60	F	HOSHIARPUR	HOUSEWIFE	N	N	N	-	N	N
38	JK	668918	45	F	JLD	HOUSEWIFE	Y (L)	Y	Y (L)	30	Y (L)	Y
39	LS	673798	34	M	JLD	TEACHER	Y(R)	Y	Y(R)	30	Y(R)	Y
40	N	682958	76	M	FEROZPUR	FARMER	Y (L)	Y	Y (L)	15	N	N

			TATION		OCULARPRESENTATION					ASSOCIATED SYMPTOMS			
SR NO	Name	mrd no	PARALYSIS	DURATION (DAYS)	LACRIMATION	PRI ORB SWELLING	PROPTOSIS	VISION LOSS	DURATION (DAYS)	HEADACH	SYSTEMIC FEVER	DM	DKA
1	R	277663	Y	60	Y(R)	Y(R)	Y(R)	Y(R)	5	Y	Y	Y	Y
2	RB	286001	N	5	N	N	N	N	-	Y	Y	N	N
3	KK	303036	N	-	N	N	N	N	-	N	Y	Y	Y
4	HS	354287	N	-	N	Y(L)	Y(L)	Y(L)	1	N	Y	Y	Y
5	VS	374362	N	-	N	Y(L)	Y(L)	Y(L)	3	Y	Y	Y	Y
6	AS	382652	N	-	N	Y(R)	N	Y(R)	5	N	N	Y	Y
7	RS	382678	Y	15	N	Y(L)	Y(L)	Y(L)	7	Y	Y	Y	Y
8	SS	383128	N	-	N	Y(L)	Y(L)	Y(L)	7	Y	Y	Y	Y
9	AK	389632	Y	90	N	Y(L)	Y(L)	Y(L)	15	N	N	Y	N
10	S	398312	N	-	N	Y(R)	Y(R)	Y(R)	3	Y	Y	Y	Y
11	S	394127	N	-	N	Y(R)	Y(R)	Y(R)	5	Y	N	Y	Y
12	NK	398224	N	5	Y	N	N	N	5	Y	Y	Y	Y
13	SS	418216	N	-	N	Y(L)	Y(L)	Y(L)	30	Y	Y	Y	Y
14	PK	423000	N	-	N	N	N	N	-	Y	N	Y	Y
15	MS	425807	N	-	Y	Y(L)	N	N	5	N	N	Y	Y
16	MB	427718	N	-	N	Y(L)	Y(L)	Y(L)	5	Y	Y	Y	Y
17	DS	429115	N	15	N	N	N	N	-	Y	N	N	N
18	PK	454441	N	15	N	Y(L)	Y(L)	Y(L)	5	N	N	Y	Y
19	Z	470575	N	10	Y	N	N	N	-	Y	Y	Y	Y
20	DS	480072	N	4	Y	Y(R)	Y(R)	Y(R)	4	Y	Y	Y	Y
21	SP	480915	N	-	N	Y(L)	Y(L)	Y(L)	4	Y	N	Y	Y
22	HS	499988	N	-	N	Y(L)	Y(L)	Y(L)	5	Y	Y	Y	Y
23	BS	509830	N	12	Y	Y(R)	Y(R)	Y(R)	12	N	N	Y	Y
24	KS	520072	Y	30	N	Y(L)	Y(L)	Y(L)	3	N	N	Y	Y
25	SS	572372	N	-	N	Y(R)	Y(R)	Y(R)	3	Y	Y	Y	Y
26	SR	582311	N	10	Y	Y(L)	Y(L)	Y(L)	4	Y	Y	Y	Y
27	HS	590598	N	-	N	Y(L)	Y(L)	Y(L)	7	Y	Y	Y	Y
28	HS	592952	N	15	N	Y(L)	Y(L)	Y(L)	2	Y	Y	Y	Y
29	DK	595181	N	30	Y	Y(L)	Y(L)	Y(L)	1	Y	Y	Y	Y
30	PJ	603251	N	15	Y	N	N	N	-	Y	Y	Y	Y
31	P	601609	N	-	N	Y(L)	Y(L)	Y(L)	4	Y	Y	Y	Y
32	TS	607346	Y	30	Y	N	N	N	-	Y	N	Y	N
33	NK	611699	N	2	N	N	N	N	-	Y	Y	Y	Y
34	P	623320	N	10	Y	Y(L)	N	Y(L)	5	Y	Y	Y	N
35	MA	631012	N	15	Y	Y(R)	Y(R)	Y(R)	15	Y	Y	Y	Y
36	R	647290	N	3	Y	Y(R)	Y(R)	Y(R)	3	Y	Y	Y	Y
37	JK	656160	N	-	N	Y(L)	Y(L)	Y(L)	1	Y	Y	Y	Y
38	JK	668918	N	15	N	N	N	N	-	Y	Y	Y	Y
39	LS	673798	N	5	Y	N	N	N	-	Y	Y	Y	Y
40	N	682958	N	-	N	N	N	N	-	Y	Y	Y	Y

			CO-MORBID STATES				RISK FACTORS				NASAL ENDOSCOPIC EVALUATION					
SR NO	Name	mrd no	TB	CKD	REACTIVE	OTHERS	ALCOHOL	SMOKER	DRUG ABUSE	STEROID USE	SEPTUM	INF TURB	MID TURB	FLOOR	MUCOSA	ESCHAR
1	R	277663	N	Y	N	N	Y	Y	N	N	Y	Y	Y	N	Y	N
2	RB	286001	N	Y	HCV	HTN	N	N	N	Y	N	N	Y	N	Y	N
3	KK	303036	N	N	N	N	N	N	N	N	N	N	N	N	Y	N
4	HS	354287	N	N	N	N	Y	N	N	N	N	N	Y	N	Y	N
5	VS	374362	N	N	N	AFI	Y	Y	Y	N	N	N	Y	N	Y	N
6	AS	382652	N	N	N	N	Y	Y	N	N	N	Y	N	N	N	N
7	RS	382678	N	N	HBV	N	N	N	N	N	Y	Y	Y	Y	Y	Y
8	SS	383128	N	N	N	DIB FOOT	Y	N	Y	N	Y	Y	Y	N	Y	Y
9	AK	389632	N	N	N	HTN	Y	Y	Y	N	Y	Y	Y	N	Y	N
10	S	398312	N	N	N	ABSCESS	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
11	S	394127	N	N	N	CAD	Y	N	Y	N	N	Y	Y	N	Y	N
12	NK	398224	N	N	N	HYPOKAL	N	N	N	Y	Y	Y	Y	N	Y	N
13	SS	418216	N	Y	N	N	Y	N	Y	N	Y	Y	Y	Y	Y	N
14	PK	423000	N	Y	N	HTN	N	N	N	Y	Y	Y	Y	Y	Y	N
15	MS	425807	N	N	N	NN	Y	Y	Y	N	Y	N	Y	N	N	N
16	MB	427718	N	N	N	LEUK	N	N	N	Y	Y	Y	Y	Y	Y	N
17	DS	429115	N	N	N	N	Y	N	N	N	N	N	N	N	N	N
18	PK	454441	Y	N	N	N	N	N	N	N	Y	Y	Y	N	Y	N
19	Z	470575	Y	N	N	N	N	N	N	N	N	Y	Y	N	Y	N
20	DS	480072	N	N	N	N	Y	Y	Y	Y	N	Y	Y	N	N	N
21	SP	480915	N	Y	N	HTN	Y	Y	Y	N	N	Y	Y	N	Y	Y
22	HS	499988	N	N	HEPC	N	Y	Y	Y	N	N	Y	N	N	N	N
23	BS	509830	N	N	N	N	Y	N	Y	N	Y	Y	N	N	N	Y
24	KS	520072	N	Y	N	EPILEPSY	Y	N	Y	N	Y	Y	Y	Y	Y	Y
25	SS	572372	N	N	N	BA/HTN	Y	Y	Y	N	N	Y	Y	N	N	N
26	SR	582311	N	N	N	N	Y	Y	Y	N	N	Y	Y	N	N	N
27	HS	590598	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	N	N
28	HS	592952	Y	Y	N	PANCREAT	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
29	DK	595181	N	N	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
30	PJ	603251	N	N	N	N	Y	Y	N	N	N	Y	Y	N	N	N
31	P	601609	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	N	N
32	TS	607346	N	N	N	N	Y	Y	N	N	Y	Y	Y	N	Y	N
33	NK	611699	N	Y	N	N	N	N	N	N	N	N	Y	N	N	N
34	P	623320	N	Y	N	N	Y	Y	Y	Y	N	Y	N	N	N	N
35	MA	631012	N	N	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N
36	R	647290	N	Y	N	N	Y	N	Y	N	Y	Y	Y	Y	Y	Y
37	JK	656160	Y	Y	HEPC	N	N	N	N	Y	Y	Y	Y	Y	Y	Y
38	JK	668918	N	N	N	N	N	N	N	N	Y	Y	Y	N	Y	N
39	LS	673798	N	N	N	N	Y	Y	Y	N	N	Y	Y	N	N	N
40	N	682958	N	N	N	CAD	Y	Y	Y	Y	N	Y	N	N	N	N

				OCULAR EXAMINATION							CRANIAL NERV		
SR NO	Name	mrd no	PALATE NECROSIS	CHEMOSIS	FUNDUS	CRAO	EOM	VL	DIPLOPIA	PUPIL REF	CRANIAL NERVE EXAMINATION_2	CRANIAL NERVE EXAMINATION_3	CRANIAL NERVE EXAMINATION_4
1	R	277663	N	Y	Y	Y	FROZEN	Y	Y	N	Y	Y	Y
2	RB	286001	N	N	N	N	N	N	N	Y	N	N	N
3	KK	303036	N	N	N	N	N	N	N	Y	N	N	N
4	HS	354287	N	Y	Y	Y	FROZEN	Y	Y	N	Y	Y	Y
5	VS	374362	N	Y	N	N	RESTRICT	Y	Y	N	N	Y	Y
6	AS	382652	N	N	N	N	N	N	N	Y	N	N	N
7	RS	382678	Y	Y	Y	Y	FROZEN	Y	Y	N	Y	Y	Y
8	SS	383128	N	Y	Y	Y	FROZEN	Y	Y	N	Y	Y	Y
9	AK	389632	N	Y	Y	Y	FROZEN	Y	Y	N	Y	Y	Y
10	S	398312	N	Y	Y	Y	FROZEN	Y	Y	N	Y	Y	Y
11	S	394127	N	Y	N	N	RESTRICT	Y	Y	Y	N	Y	Y
12	NK	398224	Y	N	N	N	N	N	N	Y	N	N	N
13	SS	418216	N	Y	Y	N	RESTRICT	Y	Y	Y	N	Y	Y
14	PK	423000	N	N	N	N	N	N	N	Y	N	N	N
15	MS	425807	N	Y	N	N	N	N	Y	Y	N	N	N
16	MB	427718	N	Y	Y	Y	FROZEN	Y	Y	N	Y	Y	Y
17	DS	429115	N	N	N	N	N	N	N	Y	N	N	N
18	PK	454441	Y	Y	Y	Y	RESTRICT	Y	Y	Y	N	Y	Y
19	Z	470575	Y	N	N	N	N	N	N	Y	N	N	N
20	DS	480072	N	Y	Y	Y	FROZEN	Y	Y	N	Y	Y	Y
21	SP	480915	N	Y	N	N	RESTRICT	Y	Y	Y	N	Y	Y
22	HS	499988	N	Y	Y	Y	FROZEN	Y	N	N	Y	Y	Y
23	BS	509830	N	Y	Y	Y	FROZEN	Y	Y	N	Y	Y	Y
24	KS	520072	Y	Y	Y	Y	FROZEN	Y	N	N	Y	Y	Y
25	SS	572372	N	Y	Y	Y	RESTRICT	N	Y	Y	N	Y	Y
26	SR	582311	N	Y	Y	Y	FROZEN	Y	Y	N	Y	Y	Y
27	HS	590598	N	Y	Y	Y	FROZEN	Y	N	N	Y	Y	Y
28	HS	592952	N	N	N	N	RESTRICT	N	Y	Y	N	Y	Y
29	DK	595181	N	Y	Y	Y	FROZEN	Y	N	N	Y	Y	Y
30	PJ	603251	N	N	N	N	N	N	N	Y	N	N	N
31	P	601609	N	Y	Y	Y	FROZEN	Y	N	N	Y	Y	Y
32	TS	607346	N	N	N	N	N	N	N	Y	N	N	N
33	NK	611699	N	N	N	N	N	N	Y	Y	N	N	N
34	P	623320	N	N	N	Y	FROZEN	Y	N	N	Y	Y	Y
35	MA	631012	N	Y	N	N	RESTRICT	N	Y	Y	N	Y	Y
36	R	647290	Y	Y	Y	Y	FROZEN	Y	N	N	Y	Y	Y
37	JK	656160	Y	Y	Y	Y	FROZEN	Y	N	N	Y	Y	Y
38	JK	668918	Y	N	N	N	N	N	N	Y	N	N	N
39	LS	673798	N	N	N	N	N	N	N	N	N	N	N
40	N	682958	Y	N	N	N	N	N	N	Y	N	N	N

			E EXAMINATION			LAB PARAMETERS				KOH EXAMINATION	
SR NO	Name	mrd no	CRANIAL NERVE EXAMINATION_5	CRANIAL NERVE EXAMINATION_6	CRANIAL NERVE EXAMINATION_7	ANAEMIA	LEUCOCYTOSIS	RENAL FUNCTN	ELECTROLYTES	SEPTATE	ASEPTATE
1	R	277663	Y	Y	Y	Y	Y	Y	Y	N	Y
2	RB	286001	Y	N	N	Y	Y	Y	y	y	N
3	KK	303036	N	N	N	N	Y	N	N	N	Y
4	HS	354287	N	Y	N	Y	Y	Y	Y	N	Y
5	VS	374362	Y	Y	N	Y	Y	N	N	Y	N
6	AS	382652	N	N	N	N	N	N	N	N	Y
7	RS	382678	Y	Y	Y	Y	Y	Y	Y	Y	N
8	SS	383128	N	Y	N	Y	Y	N	N	Y	Y
9	AK	389632	N	Y	Y	Y	Y	N	Y	Y	Y
10	S	398312	Y	Y	N	Y	Y	Y	Y	Y	Y
11	S	394127	N	Y	N	Y	Y	Y	Y	N	N
12	NK	398224	N	N	Y	Y	Y	Y	Y	Y	N
13	SS	418216	N	Y	N	Y	Y	N	N	N	Y
14	PK	423000	N	N	N	Y	Y	Y	Y	N	N
15	MS	425807	N	Y	N	Y	Y	N	N	Y	N
16	MB	427718	Y	Y	N	Y	Y	N	Y	Y	Y
17	DS	429115	Y	N	N	Y	Y	N	N	Y	N
18	PK	454441	Y	Y	N	Y	Y	N	N	N	N
19	Z	470575	N	N	N	Y	Y	Y	Y	Y	Y
20	DS	480072	N	Y	N	Y	Y	Y	Y	N	N
21	SP	480915	N	Y	N	N	Y	Y	Y	Y	N
22	HS	499988	N	Y	N	Y	Y	Y	Y	N	N
23	BS	509830	Y	Y	N	Y	Y	N	N	Y	N
24	KS	520072	N	Y	Y	Y	Y	Y	Y	N	Y
25	SS	572372	N	Y	N	Y	Y	N	Y	Y	N
26	SR	582311	Y	Y	N	Y	Y	Y	Y	Y	Y
27	HS	590598	Y	Y	N	Y	Y	N	N	Y	N
28	HS	592952	N	Y	N	Y	Y	Y	Y	N	Y
29	DK	595181	Y	Y	N	Y	Y	N	N	Y	Y
30	PJ	603251	Y	N	N	Y	Y	N	N	N	N
31	P	601609	Y	Y	N	Y	Y	N	N	Y	Y
32	TS	607346	Y	N	N	Y	Y	Y	Y	N	Y
33	NK	611699	Y	Y	N	Y	N	Y	N	Y	N
34	P	623320	Y	Y	N	Y	Y	N	Y	N	N
35	MA	631012	Y	Y	N	Y	Y	N	Y	N	Y
36	R	647290	Y	Y	N	Y	Y	Y	Y	Y	Y
37	JK	656160	Y	Y	N	Y	Y	Y	Y	N	Y
38	JK	668918	Y	N	N	Y	Y	Y	Y	N	N
39	LS	673798	N	N	N	Y	Y	Y	N	Y	N
40	N	682958	N	N	N	Y	Y	N	N	N	N

					PARANASAL SINUS INVOLVEMENT			EXTRA SINUS INVOLVEMENT		
SR NO	Name	mrd no	FUNGAL CULT	POST AMPHOTERICIN CREATININ	MUCOSAL THICKENING	SINUS WALL DESTRUCTION	HYPERDENSITY/OPACIFICATION	INFRATEMPORAL FOSSA	NASOLACRIMAL DUCT	PERINEURAL INVASION
1	R	277663	ND	2.2	N	Y	N	N	N	N
2	RB	286001	ASPERGILLUS FLAVUS	-	Y	N	N	N	N	N
3	KK	303036	MUCOR+ASPERGILLUS	1.2	N	N	Y	N	N	N
4	HS	354287	NG	2.15	N	N	Y	N	N	Y
5	VS	374362	NG	0.66	N	N	Y	N	N	N
6	AS	382652	MUCOR	0.59	Y	N	N	N	N	N
7	RS	382678	NG	1.5	N	Y	Y	N	N	N
8	SS	383128	ASPERGILLUS FLAVUS	0.58	N	Y	Y	N	N	Y
9	AK	389632	ASPERGILLUS FLAVUS	1.34	Y	Y	N	Y	N	N
10	S	398312	NG	2.1	N	N	Y	N	N	N
11	S	394127	ND	3.6	Y	N	N	N	N	N
12	NK	398224	ND	1.25	N	Y	Y	Y	N	N
13	SS	418216	NG	1	Y	N	N	N	N	N
14	PK	423000	ND	2.49	N	N	Y	N	N	N
15	MS	425807	NG	1.24	Y	N	N	N	Y	N
16	MB	427718	ASPERGILLUS FLAVUS	0.46	Y	N	N	N	N	N
17	DS	429115	ASPERGILLUS FLAVUS	0.25	Y	N	Y	N	N	N
18	PK	454441	NG	1.05	N	N	Y	Y	N	N
19	Z	470575	NG	1.8	Y	Y	N	N	N	N
20	DS	480072	ND	2.5	Y	N	N	N	N	Y
21	SP	480915	NG	1.84	N	N	Y	N	N	N
22	HS	499988	ND	0.75	Y	N	N	N	N	N
23	BS	509830	MUCOR	0.5	N	N	N	N	N	N
24	KS	520072	ASPERGILLUS FLAVUS	2.2	N	N	Y	N	N	N
25	SS	572372	ASPERGILLUS FLAVUS	1.17	N	N	Y	N	N	N
26	SR	582311	ND	0.6	Y	N	Y	N	N	N
27	HS	590598	NG	1.23	N	Y	N	N	N	N
28	HS	592952	NG	1.8	N	N	Y	N	N	N
29	DK	595181	NG	0.74	N	N	Y	N	N	N
30	PJ	603251	ND	0.76	N	N	Y	N	N	N
31	P	601609	NG	0.74	N	N	Y	N	N	N
32	TS	607346	NG	2.6	Y	N	N	N	N	N
33	NK	611699	ASPERGILLUS FLAVUS	1.2	N	N	Y	Y	N	N
34	P	623320	ND	0.89	Y	N	N	Y	N	Y
35	MA	631012	NG	0.96	Y	N	N	Y	N	N
36	R	647290	MUCOR	3.3	N	N	Y	N	N	N
37	JK	656160	MUCOR	2.8	N	N	Y	N	N	N
38	JK	668918	ND	1.9	N	N	Y	Y	N	N
39	LS	673798	ND	2.1	N	N	Y	N	N	N
40	N	682958	NG	1.2	Y	N	N	Y	N	N

SR NO	Name	mrd no	RADIOLOGICAL INVOLVEMENT							
				ORBITAL INVOLVEMENT						
			PERIVASCULAR INVASION	PROPTOSIS	CAVERNOUS SINUS THROMBOSIS	PRESEPTAL CELLULITIS	ORBITAL CELLULITIS	SEPTUM	MAXILLARY	ETHMOID
1	R	277663	N	N	Y	N	Y	DNS R	Y	Y
2	RB	286001	N	N	N	N	N	DNS R	Y	Y
3	KK	303036	N	N	N	N	N	DNS R	Y	Y
4	HS	354287	N	Y	N	Y	Y	N	Y	Y
5	VS	374362	N	N	N	N	Y	N	Y	Y
6	AS	382652	N	N	N	N	N	DNS R	Y	N
7	RS	382678	Y	Y	N	N	Y	N	Y	Y
8	SS	383128	N	N	N	N	N	N	Y	Y
9	AK	389632	N	Y	N	Y	N	N	Y	Y
10	S	398312	N	N	N	N	Y	N	Y	Y
11	S	394127	N	N	N	N	Y	N	N	Y
12	NK	398224	N	N	N	N	N	N	Y	Y
13	SS	418216	N	N	N	N	N	DNS R	Y	Y
14	PK	423000	N	N	N	N	N	DNS R	Y	Y
15	MS	425807	N	N	N	N	N	DNS R	Y	Y
16	MB	427718	N	Y	N	Y	N	N	Y	Y
17	DS	429115	N	N	N	N	N	DNS R	Y	Y
18	PK	454441	N	N	N	Y	Y	DNS R	Y	Y
19	Z	470575	N	N	N	N	N	DNS R	Y	Y
20	DS	480072	N	Y	N	N	N	DNS R	Y	Y
21	SP	480915	N	N	N	N	N	DNS R	Y	Y
22	HS	499988	N	Y	N	N	N	DNS R	Y	Y
23	BS	509830	N	Y	Y	N	Y	DNS L	Y	Y
24	KS	520072	N	Y	N	N	Y	DNS L	Y	Y
25	SS	572372	N	N	N	N	Y	DNS L	Y	Y
26	SR	582311	N	N	N	N	N	DNS R	Y	Y
27	HS	590598	N	N	N	N	N	DNS L	Y	Y
28	HS	592952	N	N	N	N	N	DNS L	Y	Y
29	DK	595181	N	N	N	N	Y	DNS R	Y	N
30	PJ	603251	N	N	N	N	N	N	Y	Y
31	P	601609	N	N	N	N	Y	DNS L	Y	Y
32	TS	607346	N	N	N	N	N	DNS L	Y	Y
33	NK	611699	N	N	N	N	N	N	Y	Y
34	P	623320	N	N	N	N	Y	DNS L	Y	Y
35	MA	631012	N	N	N	N	N	DNS R	Y	Y
36	R	647290	N	N	N	N	N	N	Y	Y
37	JK	656160	N	N	N	N	Y	DNS R	Y	Y
38	JK	668918	N	N	N	N	N	N	Y	Y
39	LS	673798	N	N	N	N	N	N	Y	Y
40	N	682958	N	N	N	N	N	N	Y	Y

							SURGICAL INTERVENTION					
SR NO	Name	mrd no	FRONTAL	SPHENOID	SIDE	INTRACRANIAL	NASAL DEBRIDEMENT	ORBITAL EXENTERATION	MAXILLECTOMY	PALATE DEBRIDEMENT	ANESTHESIA	AMPHOTERICIN B_CON
1	R	277663	Y	Y	R	Y	Y	N	N	N	MAC	N
2	RB	286001	Y	Y	R	N	Y	N	N	N	GA	N
3	KK	303036	Y	Y	R	N	Y	N	N	N	GA	Y
4	HS	354287	Y	Y	B/L	N	Y	N	N	N	GA	N
5	VS	374362	N	Y	L	N	Y	N	N	N	GA	N
6	AS	382652	N	N	R	N	Y	N	N	N	GA	Y
7	RS	382678	Y	Y	L	Y	Y	Y	Y	Y	GA	Y
8	SS	383128	N	Y	L	Y	Y	N	N	N	GA	N
9	AK	389632	N	Y	B/L	N	Y	Y	N	N	GA	Y
10	S	398312	Y	Y	R	N	Y	Y	N	N	GA	N
11	S	394127	N	N	R	N	Y	N	N	N	GA	N
12	NK	398224	Y	Y	L	N	Y	N	N	N	GA	N
13	SS	418216	Y	Y	L	N	Y	N	N	N	MAC	N
14	PK	423000	Y	Y	B/L	N	Y	N	N	N	LA	N
15	MS	425807	N	Y	L	N	Y	N	N	N	GA	N
16	MB	427718	Y	Y	B/L	Y	Y	N	N	N	MAC	N
17	DS	429115	Y	Y	B/L	N	Y	N	N	N	GA	Y
18	PK	454441	Y	Y	L	N	Y	N	Y	Y	GA	Y
19	Z	470575	N	N	L	N	Y	N	Y	Y	GA	N
20	DS	480072	Y	Y	R	Y	Y	Y	N	N	GA	Y
21	SP	480915	Y	Y	B/L	N	Y	N	N	N	GA	N
22	HS	499988	Y	Y	L	N	Y	Y	N	N	GA	N
23	BS	509830	Y	Y	R	Y	Y	N	N	Y	GA	N
24	KS	520072	Y	Y	L	N	Y	N	N	Y	MAC	N
25	SS	572372	Y	Y	L	N	Y	N	Y	N	GA	Y
26	SR	582311	Y	Y	L	N	Y	N	N	N	LA	Y
27	HS	590598	Y	Y	L	Y	Y	N	N	N	GA	Y
28	HS	592952	N	N	L	N	Y	N	N	N	GA	N
29	DK	595181	N	N	L	N	Y	N	N	N	GA	Y
30	PJ	603251	Y	Y	L	N	Y	N	N	N	GA	N
31	P	601609	Y	Y	L	N	Y	Y	N	N	GA	Y
32	TS	607346	Y	Y	B/L	N	Y	N	N	N	GA	Y
33	NK	611699	Y	Y	B/L	N	Y	N	N	N	GA	Y
34	P	623320	Y	Y	L	N	Y	N	N	N	GA	Y
35	MA	631012	Y	Y	R	N	Y	N	N	N	GA	Y
36	R	647290	Y	Y	R	N	Y	N	Y	Y	GA	Y
37	JK	656160	Y	Y	R	Y	Y	N	N	N	GA	N
38	JK	668918	Y	Y	L	N	Y	N	Y	N	GA	N
39	LS	673798	Y	Y	R	N	Y	N	N	N	GA	N
40	N	682958	Y	Y	L	N	Y	N	N	Y	LA	N

SR NO	Name	mrd no	MEDICAL THERAPEUTICS			HISTOPATHOLOGICAL EXAMINATION	POST TREATMENT FOLLOWUP			OUTCOME
			AMPHOTERICIN B_LIPO	AMPHOTERICIN B_DOSE	BOTH		FOLLOW UP_ 1ST MNT	FOLLOW UP_ 3 MNTH	FOLLOW UP_ 6 MNTH	
1	R	277663	Y	1280	Y	ZYGOMYCETES	F	F	F	SURVIVAL
2	RB	286001	N	N	N	ZYGOMYCETES	F	F	F	SURVIVAL
3	KK	303036	N	1700	Y	ZYGOMYCETES	F	F	F	SURVIVAL
4	HS	354287	Y	2900	Y	ZYGOMYCETES	F	F	F	SURVIVAL
5	VS	374362	Y	2560	Y	ZYGOMYCETES	F	F	F	SURVIVAL
6	AS	382652	N	1700	Y	ZYGOMYCETES	F	F	F	SURVIVAL
7	RS	382678	N	2010	Y	MUCORMYCOSIS	F	F	F	SURVIVAL
8	SS	383128	Y	2238	Y	MUCORMYCOSIS	F	F	F	SURVIVAL
9	AK	389632	N	2230	Y	ZYGOMYCETES	F	F	F	SURVIVAL
10	S	398312	Y	2010	Y	ZYGOMYCETES	F	F	F	SURVIVAL
11	S	394127	Y	2240	Y	MUCORMYCOSIS	F	F	F	SURVIVAL
12	NK	398224	Y	3000	Y	MUCORMYCOSIS	EXPIRED	EXPIRED	EXPIRED	EXPIRED
13	SS	418216	Y	2248	Y	ZYGOMYCETES	F	F	F	SURVIVAL
14	PK	423000	Y	2600	Y	ZYGOMYCETES	F	F	F	SURVIVAL
15	MS	425807	Y	2280	Y	ZYGOMYCETES	F	F	F	SURVIVAL
16	MB	427718	Y	2200	Y	ZYGOMYCETES	F	F	F	SURVIVAL
17	DS	429115	N	1180	Y	ZYGOMYCETES	F	F	F	SURVIVAL
18	PK	454441	N	1280	Y	ZYGOMYCETES	F	F	F	SURVIVAL
19	Z	470575	Y	1500	Y	MUCORMYCOSIS	F	F	F	SURVIVAL
20	DS	480072	N	1800	Y	MUCORMYCOSIS	F	F	F	SURVIVAL
21	SP	480915	Y	600	Y	ZYGOMYCETES	-			
22	HS	499988	Y	1800	Y	ZYGOMYCETES	F	F	F	SURVIVAL
23	BS	509830	Y	2380	Y	ZYGOMYCETES	F	F	F	SURVIVAL
24	KS	520072	Y	600	Y	ZYGOMYCETES	EXPIRED	EXPIRED	EXPIRED	EXPIRED
25	SS	572372	N	2280	Y	MUCORMYCOSIS	F	F	F	SURVIVAL
26	SR	582311	N	450	Y	ZYGOMYCETES	-			
27	HS	590598	N	2000	Y	ZYGOMYCETES	F	F	F	SURVIVAL
28	HS	592952	Y	1850	Y	ZYGOMYCETES	F	F	F	SURVIVAL
29	DK	595181	N	1300	Y	ZYGOMYCETES	-			
30	PJ	603251	Y	2200	Y	ZYGOMYCETES	F	F	F	SURVIVAL
31	P	601609	N	1840	Y	ZYGOMYCETES	F	F	F	SURVIVAL
32	TS	607346	N	850	Y	ZYGOMYCETES	F	F	F	SURVIVAL
33	NK	611699	N	2280	Y	ZYGOMYCETES	F	F	F	SURVIVAL
34	P	623320	N	1100	Y	ZYGOMYCETES	F	F	F	SURVIVAL
35	MA	631012	N	750	-	ZYGOMYCETES	-			
36	R	647290	N	2290	Y	ZYGOMYCETES	EXPIRED	EXPIRED	EXPIRED	EXPIRED
37	JK	656160	Y	800	Y	ZYGOMYCETES	EXPIRED	EXPIRED	EXPIRED	EXPIRED
38	JK	668918	Y	3000	Y	ZYGOMYCETES	F	F	F	SURVIVAL
39	LS	673798	Y	2200	Y	ZYGOMYCETES	-			
40	N	682958	Y	2560	Y	ZYGOMYCETES	F	F	F	SURVIVAL

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No. BFUHS/2K18p-TH/ 14220 **Date** 5/X/18

The Principal,
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 31.08.2018 has approved the plan of thesis of Dr. Porshia Rishi, a student of your college for **MS Otorhinolaryngology (ENT)** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Sinonasal mucormycosis: clinical profile and outcome

Supervisor
Dr. Manish Munjal
Prof. & Head,
Dept. of ENT,
DMCH, Ludhiana.

Co-Supervisor
Dr. Veenu Gupta
Prof.,
Dept. of Microbiology,
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DMCH, Ludhiana..

The student may submit the four copies of thesis, to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She may be directed to attach a photocopy of this letter with the forwarding letter while submitting thesis in the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic, if any.

S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

1. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*
2. *The student may submit the thesis as per the schedule already conveyed i.e for May/June examination 30th Nov of the preceding the year of examination and for Nov/Dec examinations 31st May of the year of examination.*

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No. BFUHS/2K18p-TH/_____ **Date_____**

The Principal.
DMC, Ludhiana.

Subject: **Approval of Plan of Thesis.**

This is to inform you that the Faculty of Medical Sciences in its meeting held on 31.08.2018 has approved the plan of thesis of Dr. Porshia Rishi, a student of your college for **MS Otorhinolaryngology (ENT)** along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Sinonasal mucormycosis: clinical profile and outcome

Supervisor
Dr. Manish Munjal
Prof. & Head,
Dept. of ENT,
DMCH, Ludhiana.

Co-Supervisor
Dr. Veenu Gupta
Prof.,
Dept. of Microbiology,
DMCH, Ludhiana.

Dr. Amit Bery
Assoc. Prof.,
Dept. of Medicine,
DMCH, Ludhiana..

The student may submit the four copies of thesis, to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She may be directed to attach a photocopy of this letter with the forwarding letter while submitting thesis in the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic, if any.

S P Singh

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

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SINONASAL MUCORMYCOSIS:

CLINICAL PROFILE AND OUTCOME

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED IN

PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MS

In

ENT

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES

FARIDKOT

JANUARY, 2018

DR. PORSHIA RISHI

DEPARTMENT OF ENT

DAYANAND MEDICAL COLLEGE AND HOSPITAL

LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	SINONASAL MUCORMYCOSIS:CLINICAL PROFILE AND OUTCOME
For the degree of	MS (ENT)
Name of the candidate	Dr. Porshia Rishi
Supervisor	Dr Manish Munjal
Co-supervisor(s)	Dr.Veenu Gupta, Professor, Department of Microbiology, DMCH, Ludhiana Dr. Amit Bery, Associate Professor, department of Medicine, DMCH, Ludhiana
Institution	Dayanand Medical College and Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Mucormycosis, a serious angioinvasive infection caused by common filamentous fungi, that is, mucormycetes, constitutes the third most common invasive fungal infection following aspergillosis and candidiasis. Sinonasal mucormycosis if unrecognized or inadequately treated is an acutely fatal fungal infection. The outcome of the patient with sinonasal mucormycosis depends on (1) early diagnosis, (2) reversal of the predisposing risk factors, (3) appropriate early surgical debridement (4) Rapid Antifungal therapy.

Aims & Objectives: a) To study the clinical presentation of sinonasal mucormycosis. b) To study the association of various comorbidities associated with sinonasal mucormycosis.c) To evaluate the outcome of surgical and medical interventions in sinonasal mucormycosis.

Material & Methods: In this prospective clinical study the patients admitted with microbiologically/histopathologically proven sinonasal mucormycosis over a period of 1 year (Jan 2018 to Dec 2018) undergoing surgical and medical intervention at the department of ENT and Head & Neck surgery DMC & Hospital Ludhiana will be studied.

Clinical Significance: This study tends to evaluate the outcome of the patient proven to be microbiologically/histopathologically proven sinonasal mucormycosis undergoing surgical and medical interventions at DMCH.

Keywords: Surgical Debridement, Sinonasal Mucormycosis, Amphotericin B.

(Signature)	(Signature)	(Signature)	(Signature)	(Signature)
Candidate	Co-supervisor	Co-supervisor	Supervisor	Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"SINONASAL MUCORMYCOSIS: CLINICAL PROFILE AND OUTCOME"** exist in the Department of ENT, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate herself under our supervision and guidance.

Supervisor

Dr. Manish Munjal
Professor & Head
Department of ENT
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Co-Supervisor(s)

Dr. Veenu Gupta
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Dr. Manish Munjal
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DMCH, Ludhiana

Place : Ludhiana

Date : 19/1/2019

APPROVAL PROFORMA
BY
RESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Porshia Rishi
Department	ENT
Topic of Thesis	SINONASAL MUCORMYCOSIS :CLINICAL PROFILE AND OUTCOME
Likely date of appearing in PG examination	May 2020
Date of enrollment	31st May, 2017
Name of Head of Department	Dr. Manish Munjal
1) Supervisor	Dr. Manish Munjal
2) Co-Supervisor(s)	Dr. Veenu Gupta Dr. Amit Bery

Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
1. HOD Pharmacology	1. HOD Physiology
2. HOD Surgery	2. HOD Pathology
3. HOD Pathology	3. HOD Pharmacology
4. HOD Medicine	4. HOD SPM
5. Dean Academics	5. HOD Medicine
6. Vice Principal	6. HOD Surgery
	7. HOD Obst. & Gynae.
	8. Legal Expert
	9. Secretary, IEC
	10. Dean Academics
	11. Vice Principal
	12. Principal

Approved : Yes / No
Chairperson
Research Committee

Approved : Yes / No
Chairperson
Ethics Committee

BABA FARID UNIVERSITY OF HEALTH SCIENCES, FARIDKOT

PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	DR. PORSHIA RISHI 21-H, MAJITHIA ENCLAVE, NEAR 24 NO. PHATAK, PATIALA, PUNJAB
2	NAME OF THE INSTITUTE	Dayanand Medical College and Hospital, Ludhiana
3	COURSE OF STUDY AND SUBJECT	MS ENT
4	DATE OF ADMISSION OF COURSE	31-05-2017
5	TITLE OF THE TOPIC	SINONASAL MUCORMYCOSIS:CLINICAL PROFILE AND OUTCOME

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Mucormycosis, a serious angioinvasive infection caused by common filamentous fungi, that is, mucormycetes, constitutes the third most common invasive fungal infection following aspergillosis and candidiasis.[1] The Mucormycetes are characterized by the presence of broad aseptate hyphae and are deposited by air borne mode in the nasal cavity and propelled into paranasal sinuses by ciliary action .Mucor, rhizopus and Absidia are the common species.

Sinonasal mucormycosis if unrecognized or inadequately treated is an acutely fatal fungal infection. It can infect CNS, GIT and Skin (in burn patient), but best known for it's rhinocerebral presentation, which is initiated with sinonasal involvement and may progress to involve orbit and brain.[2]

Sinonasal mucormycosis is a relatively uncommon disease which primarily affects diabetics, but can occur in any immunocompromised individual such as patient with neutropenia, leukemia, Chronic renal failure, long term systemic steroid therapy, protein-calorie malnutrition, solid organ and bone marrow transplantee, leukemia, intravenous drug abusers and having other immunodeficiency states. Once the spores enter the tissue it becomes angioinvasive and shows predilection for internal elastic lamina of arteries, veins and lymphatics. The invasion causes extensive endothelial damage, thrombosis with secondary ischemic infarction and hemorrhagic necrosis. The organism thrives in necrotic tissue and spread by direct extension along injured blood vessels.[3]

The outcome of the patient with sinonasal mucormycosis depends on

(1) early diagnosis,

(2) reversal of the predisposing risk factors,

(3) appropriate early surgical debridement

(4) Rapid Antifungal therapy

Most of the studies done on this emerging disease in India, as well as investigations throughout the world, are retrospective. Due to increase in number of cases and diverse risk factors , there is need of prospective study so that suspected cases can be diagnosed and treated in a timely manner, , which should result in the increase of patient survival. This study has been planned to study the clinical presentation, epidemiology, therapeutic medical and surgical interventions, various associated comorbidities and outcome of sinonasal mucormycosis.

6.2 REVIEW OF LITERATURE

Mucormycosis was first reported as a cause of human disease in 1885.[4]

The disease begins in the nasal cavity and paranasal sinuses. It develops through direct extension or haematogenous dissemination towards the palate, pharynx and orbit, with later intracranial dissemination by invasion through the superior orbital fissure, ophthalmic veins, cribriform plate or carotid.

In a study conducted by Roden et al on 929 cases found out that compromise of the paranasal sinuses was the most common form of infection representing 39% of cases. These cases presented with lesions in the nose, paranasal sinuses(Maxillary sinus being most commonly affected), orbit and cavernous sinus. Various risk factors are associated with the development of mucormycosis most common being in uncontrolled diabetes, ketoacidosis is considered the key factor for predisposition to mucormycosis infection.[5]

In a review of 179 cases by Diwakar *et al.* on paranasal sinus mucormycosis, 70% of patients had diabetic ketoacidosis in 2007.[6]

The study done by Chakrabarti *et al.* in 2009 reported that nearly 50% patients had uncontrolled diabetes mellitus and the association was significant (OR = 9.3; $P \leq 0.001$).[7]

Bala *et al.* studied 38 patients of mucormycosis in 2014 and found out that diabetes mellitus (56%) was the most common risk factor followed by intramuscular injection (10%), incision and drainage (5%), deferoxamine therapy (2%), and trauma (2%), and in 24% cases no risk factor was identified.[8]

In a retrospective, longitudinal, descriptive study, conducted by Hernández OP et al in 2013 the records of patients with rhino-orbital mucormycosis in the period from January to October 2013 were studied and analysed .

The time between symptom onset until the patients sought medical attention was from 4 to 30 days; 100% of the patients began with ophthalmological symptomology, with orbital apex syndrome being found in 60%. The most frequent otorhinolaryngological signs and symptoms were nasal obstruction, pale turbinates and nasal crusting (80%), facial hypoesthesia (60%) and facial paralysis (40%), while 1 patient (20%) had necrotic eschar in the palate.[9]

Other reported Risk factors include prolonged neutropenia and use of corticosteroids, hematological malignancies (leukemia, lymphoma, and multiple myeloma), Aplastic anaemia, Myelodysplastic syndromes, solid organ or hematopoietic stem cell transplantation, human immunodeficiency virus (HIV) infection, diabetic and metabolic acidosis, intravenous drug abuse, prematurity, and advanced age.[10 11]

Clinical manifestations may start with necrosis of the palate or sinuses, which may progress towards the orbit before reaching intra-cranial structures.[12 13]

Patients of Sinonasal mucormycosis initially present with nonspecific symptoms that include eye or facial pain and facial numbness followed by the onset of conjunctival suffusion, blurry vision, and soft tissue swelling.

If untreated, the infection can spread from the ethmoid sinus to the orbit, affecting extraocular muscle function and being associated with proptosis and chemosis.

The visual appearance of infected tissue may progress from normal to erythematous to violaceous to a necrotic black eschar. Black sores on the

palate or nasal mucosa are very suggestive of mucormycosis in the appropriate clinical context, although they may not be present in 50% of cases.[14.15]

The main stays of treatment for mucormycosis of the paranasal sinuses are reversal of immunocompromised state, systemic and topical amphotericin-B and surgical debridement. The first goal of therapy is control of underlying disease process.

Seiff et al. considered that local irrigations with amphotericin B are useful as adjuvant therapy in the control of rhino-orbital fungal infections, especially in patients with a reversible immunocompromised state.[16]

Orbital exenteration, together with debridement of the pterygopalatine and superior orbital fissures, should be performed in patients with progressive ocular involvement, to eliminate the fungal reservoir and prevent intracranial invasion.

Hargrove et al. reported that patients with the same symptomology and factors of risk, when exenterated, have a higher survival rate.[17]

The overall mortality rate was observed to be 46% in the largest meta-analysis done by Roden et al. in 2005 [18] and was 45% of 53 patients treated in study carried by Chakrabarti et al.[19]

The overall rate of mortality of mucormycosis is approximately 40%, but this rate depends on the clinical presentation of the disease, the underlying disease, surgery, and the extent of the infection.[20-22]

Indicators of poor prognosis include a delay in treatment , evidence of intra-cranial invasion, bilateral involvement, invasion of the palate, and the presence of haematological malignancies and any immunocompromised state

In the study conducted by Bala *et al.* in 2014 found out that Combination of surgery and medical treatment with amphotericin B was significantly better (OR = 0.2, P < 0.04) than amphotericin B alone (61.5% vs. 10.3% patient survival). A total of 31 patients were managed by surgical intervention, of which 11 patients were managed by functional endoscopic sinus surgery (FESS) and in one patient orbital exenteration was done. Two patients of oroantral fistula were managed by doing antroraphy, and in 13 patients surgical debridement was performed there was difference between survival rate when comparison between liposomal amphotericin B and conventional amphotericin B was done (88% survival vs. 66% survival). The overall mortality rate was 23% of these 38 patients treated and 62% patients survived after therapy, but there is no information about 15% patients as they left against medical advice.[8]

6.3 AIMS AND OBJECTIVES OF THE STUDY

- To study the clinical presentation of sinonasal mucormycosis.
- To study the association of various comorbities associated with sinonasal mucormycosis.
- To evaluate the outcome of surgical and medical interventions in sinonasal mucormycosis.

7. MATERIALS AND METHODS

7.1 Source of Data

In this prospective clinical study the patients admitted with microbiologically/histopathologically proven sinonasal mucormycosis over a period of 1 year (January 2018 to December 2018) undergoing surgical and medical intervention at the department of ENT and Head & Neck surgery DMC & Hospital Ludhiana will be studied.

7.2 METHOD OF COLLECTION OF DATA

INCLUSION CRITERIA

All patients presenting in various clinical departments over a period of 1 year (January 2018 to December 2018) who will be histopathologically/ microbiologiclly proven to be Sinonasal mucormycosis will be included in the study.

Enrolled patients will comprise of both immunocompromised and immunocompetent individuals.

Study would be conducted regardless of age and gender. Patient would be followed up after one, three and six months.

EXCLUSION CRITERIA

1. Patients proven with Bacterial and fungal sinusitis other than Mucormycosis

With use of all available data:

1. History of the patient: The case histories of the patients with mucormycosis will be analyzed prospectively regarding site of involvement, underlying disease, biochemical and haematological

investigations, clinical course, mode of diagnosis, agents isolated, treatment instituted, and outcome of disease.

2. Clinical examination: general physical examination, ENT examination, complete ophthalmological examination and cranial nerve 3,4,6,7 examination and nasal endoscopic examination will be done.

3. Radiological assessment: magnetic resonance imaging / computed tomography to evaluate the extent of disease

4. Microbiological examination: KOH smear /fungal culture.

-Nasal specimen- nasal secretions, nasal mucosa, crusts, nasal scrapings, excised nasal polyp/tissue biopsy will be collected and transported in saline in a sterile ,screw shaped container

-KOH MOUNT-for nasal secretions/scrapings 10-20% KOH and for biopsies 40% KOH will be used.

-FUNGAL CULTURE- SABOURAUD DEXTROSE AGAR Medium will be used

5. Treatment Modality given: this includes

1. Surgical Debridement – Radical/Local, with/without orbital exenteration

2. Amphotericin B alone

3. Amphotericin B with surgical debridement

6. Histopathological assessment of debrided tissue

7. Postoperative assessment will be done to know the outcome of disease and any complications

DURATION OF STUDY-

In this prospective clinical study the patients admitted with microbiologically/ histopathologically proven sinonasal mucormycosis over a period of 1 year (January 2018 to December 2018) undergoing surgical and medical

intervention at the department of ENT and Head & Neck surgery DMC & Hospital Ludhiana will be studied.

Outcome- various observations and results of the study will be the outcome and will be discussed thoroughly after completion of study

STATISTICAL ANALYSIS

Data will be described in terms of range, mean±standard deviation (±SD), frequencies (No of cases) and relative frequencies (%age) as appropriate.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Yes INVESTIGATIONS TO BE CONDUCTED IN PATIENTS –

1. Clinical examination: General physical examination, ENT examination, complete ophthalmological examination and 3,4,6,7 cranial nerve examination.
2. Endoscopy: Diagnostic nasal endoscopy will be done.
3. Radiological assesment: magnetic resonance imaging / computed tomography.
4. Microbiological examination: KOH smear / fungal culture.
5. Histopathological assessment of debrided tissue
6. Routine investigations to exclude any cormorbidity
7. Renal function tests

7.4 HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

Attached herewith

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PROFORMA

Sr. No.

NAME AGE/SEX

ADMISSION NO. MRD NO.

DOA DOD

ADDRESS

CHIEF COMPLAINTS -

1. NASAL SYMPTOMS- DURATION

NASAL OBSTRUCTION

NASAL DISCHARGE

NASAL BLEED

NASAL CRUSTING

2.PARANASAL SYMPTOMS - DURATION

FACIAL SWELLING

FACIAL HYPOESTHESIA

Signature of the Candidate **Signature of Supervisor**

FACIAL PARALYSIS

FACIAL TENDERNESS

3.OCULAR SYMPTOMS- DURATION

VISION : AQUITY/COLOUR VISION/BLURRING

PROPTOSIS

PERIORBITAL SWELLING

HISTORY -

BLURRING OF VISION

PERIORBITAL SWELLING

NASAL DISCHARGE -ONSET/DURATION/PROGRESSION/FACTORS

NASAL OBSTRUCTION -SITE

NASAL BLEED

ANOSMIA

THROAT PAIN OR IRRITATION

POST NASAL DRIP

HEADACHE SITE

Signature of the Candidate **Signature of Supervisor**

RADIATION

ASSOCIATED SYMPTOMS

FEVER GRADE

RIGORS AND CHILLS

ANY COMORBIDITY /IMMUNOCOMPROMISED STATE

EXAMINATION

EXTERNAL NASAL SKIN

ANY EXTERNAL NASAL DEFORMITY

ANTERIOR RHINOSCOPY: NASAL PASSAGE

SEPTUM

FLOOR OF NOSE

LATERAL WALL OF NOSE

COLOUR OF MUCOSA

TURBINATE HYPERTROPHY

DISCHARGE

CRUSTS

MASS

Signature of the Candidate **Signature of Supervisor**

POSTERIOR RHINOSCOPY- CHOANA

POSTERIOR END OF TURBINATES

PALATAL EXAMINATION

OPTHALMOLOGICAL EXAMINATION

EYELIDS

IRIS

SCLERA

CORNEA

FUNDUS

OCULAR MOVEMENTS

PERIMETRY

FUNDUS

CRANIAL NERVE EXAMINATION-3,4,6,7

PUPIL STATUS

DIPLOPIA

CONTRALATERAL EYE STATUS

Signature of the Candidate **Signature of Supervisor**

INVESTIGATIONS :

LAB REPORTS

HEMOGLOBIN

TLC

DLC

PLATELET COUNT

UREA

CREATININE

SODIUM

POTASSIUM

CHLORIDE

PT

INR

CHEST X RAY

ECG

KOH / FUNGAL CULTURE

MRI

Signature of the Candidate **Signature of Supervisor**

CT SCAN

TREATMENT MODALITY GIVEN-

SURGICAL DEBRIDEMENT - LOCAL/RADICAL

- WITH OR WITHOUT ORBITAL EXENTERATION

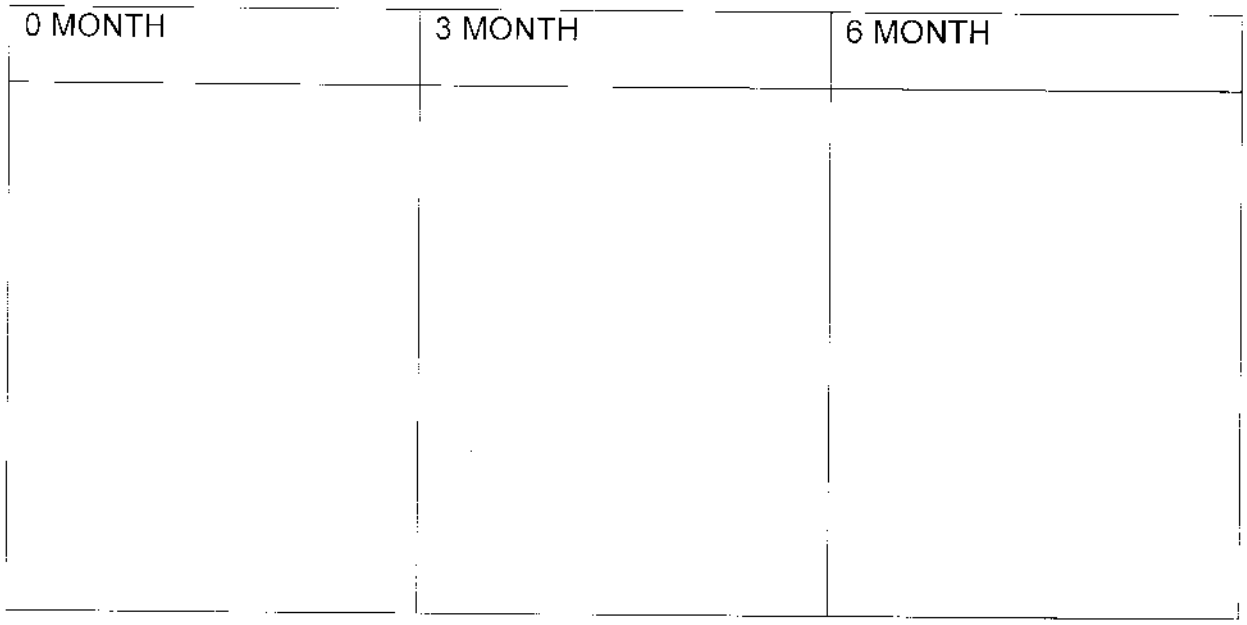
AMPHOTERICIN B - TYPE

-DOSE

SURGICAL DEBRIDEMENT + AMPHOTERICIN B

HISTOPATHOLOGICAL EXAMINATION OF DEBRIDED TISSUE

POST OPERATIVE EXAMINATION : ENDOSCOPY



OUTCOME:

Signature of the Candidate **Signature of Supervisor**

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o..... .....am willing to participate in the study **"SINONASAL MUCORMYCOSIS: CLINICAL PROFILE AND OUTCOME"** The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

....

Signature of the Witness Signature of the patient

Name:

Signature of Candidate **Signature of Supervisor**

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य "**SINONASAL MUCORMYCOSIS: CLINICAL PROFILE AND OUTCOME**" में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टि करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देश्य स्पष्ट कर दिया गया है और मुझे यह विश्वास है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्त कर सकता/सकती हूँ और मेरे अस्वीकृति व्यक्त करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक के हस्ताक्षर

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विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

"SINONASAL MUCORMYCOSIS: CLINICAL PROFILE AND OUTCOME" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾ ਮਨੋਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

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ਗਵਾਹ ਦੇ ਹਸਤਾਖਰ ਮਰੀਜ਼ ਦੇ ਹਸਤਾਖਰ

ਮਿਤੀ_____ ਮਿਤੀ_____

ਪਤਾ _____ ਪਤਾ _____

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ਨਿਰੀਖਕ ਦੇ ਹਸਤਾਖਰ

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ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ